

# **DOCUMENTO PRINCIPAL**



Dossiê técnico para submissão à CONITEC:  
**VOXZOGO<sup>®</sup> (vosoritida)** para o tratamento de  
pacientes com acondroplasia a partir de 6 meses  
de idade e cujas epífises não estão fechadas

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## RESUMO EXECUTIVO

### Introdução

A acondroplasia é uma condição multissistêmica e crônica que se caracteriza pelo crescimento ósseo endocondral deficiente. É classificada como um transtorno genético autossômico dominante, progressivo e raro, que afeta aproximadamente 250.000 pessoas em todo o mundo, sendo causada por mutação no gene FGFR3 [1]. No Brasil, estima-se cerca de 7.600 pessoas com acondroplasia, das quais aproximadamente 1.500 são menores de 18 anos [2]. A condição é tipicamente reconhecida pela baixa estatura desproporcional, que se acumula desde o nascimento até o fechamento das epífises, e causa uma série de complicações ortopédicas, neurológicas, respiratórias e cardiovasculares, que comprometem a funcionalidade, mobilidade, independência e qualidade de vida dos pacientes e de suas famílias, gerando uma significativa carga emocional, psicológica e financeira [2-6] .

Até recentemente, o manejo da acondroplasia era restrito ao tratamento sintomático e de complicações, sem abordar a causa subjacente da doença. A vosoritida (VOXZOGO®) é o primeiro e único tratamento aprovado pela ANVISA que atua diretamente na fisiopatologia da acondroplasia, promovendo o crescimento ósseo endocondral e melhorando desfechos clínicos relevantes, incluindo a qualidade de vida e funcionalidade [7]. Com base em seu extenso programa de desenvolvimento clínico, com mais de 7 anos de acompanhamento, e na experiência de vida real, a vosoritida é recomendada como padrão de tratamento da acondroplasia por diretrizes internacionais e nacionais.

Este dossiê tem como objetivo apresentar as evidências clínicas, econômicas e de impacto orçamentário que fundamentam a solicitação de incorporação da vosoritida ao SUS para o tratamento de pacientes com acondroplasia a partir de 6 meses de idade e cujas epífises não estão fechadas.



## **Contexto da Doença e Impacto**

### **Etiologia e Fisiopatologia**

A acondroplasia é causada por mutações de ganho de função no gene FGFR3, levando à inibição do crescimento ósseo endocondral [8-10]. Isso resulta em baixa estatura desproporcional e múltiplas complicações sistêmicas [1, 11, 12].

### **Características Clínicas**

- Baixa estatura desproporcional (adultos: ~124 cm mulheres, ~133 cm homens) [13-15]
- Membros curtos, macrocefalia, recuo médio-facial, cifose toracolombar, hiperflexibilidade articular [1, 16]
- Complicações ortopédicas (e.g., genu varo, cifose), neurológicas (e.g., estenose do forame magno), respiratórias (e.g., apneia obstrutiva do sono), auditivas (e.g., otite média de repetição) e cardiovasculares (i.e., risco de morte por evento cardiovascular aumentado em 10 vezes) [4, 17-19]
- Alta prevalência de dor crônica, déficit funcional e dependência para atividades diárias [4, 20, 21]
- Maior risco de mortalidade infantil, especialmente nos primeiros anos de vida, e expectativa de vida reduzida [1, 22]

### **Impacto na Qualidade de Vida e Funcionalidade**

- Redução significativa da qualidade de vida física, social e emocional, incluindo estigma social por toda a vida [5, 6, 23-25]
- Limitações em funcionalidade, autonomia, mobilidade, autocuidado, desempenho escolar e empregabilidade [21, 26-28]
- Alto impacto na vida de cuidadores e familiares [6, 23, 29-31]

### **Impacto Econômico**

- Uso intensivo de recursos de saúde (cirurgias, internações, terapias), com carga cirúrgica 10 vezes maior que a média populacional [27, 32]
- Perda de produtividade de pacientes e cuidadores [27, 28, 33]
- Custos diretos e indiretos elevados para o sistema de saúde [32]



## Necessidade Médica Não Atendida

- Ausência de tratamento farmacológico eficaz que atuasse na causa da doença até a aprovação da vosoritida [1, 12, 34]
- Manejo atual restrito a intervenções sintomáticas e cirúrgicas, com alto ônus físico, emocional e financeiro [35-37]
- Diretrizes nacionais (Sociedade Brasileira de Pediatria - SBP) e internacionais reconhecem a vosoritida como padrão ouro para o tratamento etiológico da acondroplasia [34, 38]

## Descrição da Tecnologia Proposta

- VOXZOGO® (vosoritida): Peptídeo natriurético tipo C modificado, administrado por via subcutânea diária em ambiente domiciliar, indicado para pacientes a partir de 6 meses de idade e epífises abertas [7]
- Mecanismo de ação: Antagoniza a sinalização do FGFR3, promovendo crescimento ósseo endocondral [7, 8, 39]
- Segurança: Perfil favorável, com eventos adversos leves e transitórios, principalmente reações no local da injeção [40-43]

## Evidências Clínicas

- A metodologia da revisão sistemática de literatura envolveu buscas estruturadas nas bases PubMed, Embase e Cochrane Library, com critérios de inclusão para revisões sistemáticas, ensaios clínicos de fase II/III e estudos de vida real sobre vosoritida em acondroplasia; foram incluídos 7 publicações principais (4 do estudo fase III 111-301/302, 1 do fase II 111-202, 1 do fase II 111-206 e 1 estudo de vida real), além de evidências complementares de apresentações em congressos e dados de mundo real não publicados em periódicos indexados
- Estudos de fase II e III, incluindo estudos randomizados e controlados, demonstram aumento significativo na velocidade de crescimento anualizada (VCA), escore Z de altura e proporcionalidade corporal [40-43]
  - Fase III 111-301 (5–18 anos; 1 ano) — +1,57 cm/ano na VCA vs. placebo (IC95% 1,22–1,93); melhora do escore Z de altura e sinal de proporcionalidade corporal [41].
  - Fase II 111-206 (6–24 m; 24–60 m; 1 ano) — Dif. LS na VCA +0,63 (–0,60;1,87) a +1,10 (0,13;2,07) vs. placebo; vs. história natural: +2,23



(1,24;3,22) e +1,79–1,87 (1,15;2,44 / 1,22;2,53) cm/ano; ganho refletido no Escore Z[42].

- Fase II 111-208 (6–24 m; 24–60 m; 1 ano; controle por história natural) — +2,62 (1,40;3,83) e +1,87 (1,22;2,53) cm/ano na VCA vs. história natural; aumento sustentado de CXM e do escore Z de altura [40].
- Análise de proporcionalidade corporal (programa clínico agregado) — Melhora do equilíbrio axial/apendicular (↓ índice segmento superior/inferior; ↓ altura sentada/altura total), consistente com ↑ VCA e ↑ escore Z, com efeito mais pronunciado quando iniciado precocemente [43].
- Após 4 anos de acompanhamento, a extensão do estudo 111-302 mostrou que crianças tratadas com vosoritida atingiram velocidade de crescimento anual semelhante à de crianças sem acondroplasia, com ganho adicional estimado de 20 cm (meninos) e 16 cm (meninas) em 11 anos [44]
- Melhora sustentada em qualidade de vida (QoLISSY, PedsQL) [21, 25, 44]
  - QoLISSY mostrou melhora após 3 anos: domínio físico +6,3 (auto-reportado)/+6,0 (cuidador) e social +6,8/+2,9; efeitos mais pronunciados em quem ganhou  $\geq 1$  SD no Escore Z de altura (coorte com ~4 anos de tratamento).
- Evidências de mundo real confirmam eficácia e segurança em diferentes populações, incluindo coortes brasileiras [26, 45-47]
- Perfil de segurança consistente, sem aumento de eventos adversos graves e altas taxas de adesão ao tratamento [40, 42, 43]

### **Avaliação Econômica**

- Modelo de custo-utilidade individual, perspectiva SUS, horizonte vitalício [136]
- Ganho incremental de 6,3 QALYs, custo incremental de R\$ 6.686.704,48, RCEI de R\$ R\$ 1.062.627,18/QALY [Tabela 26]
- Análises de sensibilidade confirmam robustez dos resultados [Figura 37][Figura 38]

### **Impacto Orçamentário**

- Impacto acumulado de R\$ 2,4 bilhões em 5 anos para 816 pacientes tratados [Tabela 37]



- Cenários alternativos simulam diferentes taxas de acesso e participação de mercado [Tabela 39][Tabela 41]
- Alta previsibilidade, devido às altas taxas de diagnóstico e duração limitada e pré-definida do tratamento
- Modelo e premissas conservadores, pois não consideram economias de custos diretos e indiretos, que ocorrerão tanto em 5 anos quanto no longo prazo

### **Recomendações de Agências de ATS**

- Incorporação positiva em países como França, Alemanha, Austrália, Espanha, Itália e Polônia [Tabela 42]
- Reconhecimento internacional da vosoritida como padrão de tratamento etiológico

### **Considerações Finais**

A vosoritida é um tratamento de curto prazo, administrado na infância, que proporciona benefícios a longo prazo e para toda a vida, aliviando o impacto da acondroplasia na vida dos pacientes e de suas famílias, cuidadores e sistemas de saúde. A introdução da vosoritida representa uma inovação disruptiva no manejo da doença, com benefícios comprovados por evidências de alta qualidade e sustentados em longo prazo em aspectos clínicos (ganho de altura e velocidade de crescimento, proporcionalidade, redução de complicações e maior qualidade de vida), funcionais (autonomia e atividades da vida diária), psicossociais e econômicos [41, 42, 44-47]. Complementarmente, a BioMarin conduz no Brasil o estudo de mundo real 111-606 (fase IV, observacional, multicêntrico; coorte ambispectiva) para avaliar efetividade e segurança da vosoritida na prática clínica, evidenciando investimento local alinhado ao seu reconhecimento como padrão de tratamento e oferecendo base para eventual monitoramento. Sua incorporação ao SUS tem potencial de transformar a vida de pacientes e famílias, promovendo equidade, inclusão e benefício social.

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## LISTA DE ABREVIÇÕES

AAP	Academia Americana de Pediatria
AFA	Altura adulta final
ALP	Fosfatase alcalina
ANCOVA	Análise de covariância
ANVISA	Agência Nacional de Vigilância Sanitária
CDC	Centros de Controle e Prevenção de Doenças dos Estados Unidos
CNP	Peptídeo natriurético tipo C
CNP22	CNP Nativo
DNA	Ácido desoxirribonucleico
DP	Desvio padrão
ECLAMC	Estudo Colaborativo Americano de Malformações Congênitas
EQ-5D	EuroQol 5 Dimensions
FGF	Fator de crescimento de fibroblastos
<i>FGFR3</i>	Receptor 3 do fator de crescimento de fibroblasto
GRB2	Proteína 2 ligada ao receptor do fator de crescimento
IC	Intervalo de confiança
IMC	Índice de massa corporal
IQR	Alcance interquartil
LIAISE	Estudo do Impacto da Acondroplasia ao Longo da Vida na Europa
LS	Média dos Mínimos quadrados (do inglês, least squares)
MAPK	Proteína quinase ativada por mitogênio
MedDRA	Dicionário Médico para Atividades Regulatórias
N/A	Não aplicável
NPPC	Precursor C do peptídeo natriurético
NPR-B	Precursor B do peptídeo natriurético
ORL	Ouvido, nariz e garganta
PedsQL	Inventário Pediátrico de Qualidade de Vida
QoLISSY	Qualidade de Vida em Jovens de Baixa Estatura
RCEI	Razão de custo-efetividade incremental
VCA	Velocidade de crescimento anualizada
WeeFIM	Medida de Independência Funcional versão pediátrica

## 1. ACONDROPLASIA

A acondroplasia é uma doença (CID Q77.4) genética rara, multissistêmica, progressiva e crônica que causa a inibição do crescimento ósseo endocondral, resultando em baixa estatura desproporcional e crescimento ósseo anormal que se acumulam desde o nascimento, causando uma variedade de sintomas graves e debilitantes e complicações ao longo da vida [12, 48, 49].

Devido ao crescimento ósseo endocondral anormal, os pacientes com acondroplasia apresentam maior risco de mortalidade infantil e uma expectativa de vida geral reduzida em comparação com indivíduos não afetados [22, 48].

### 1.1 Etiologia e fisiopatologia da acondroplasia

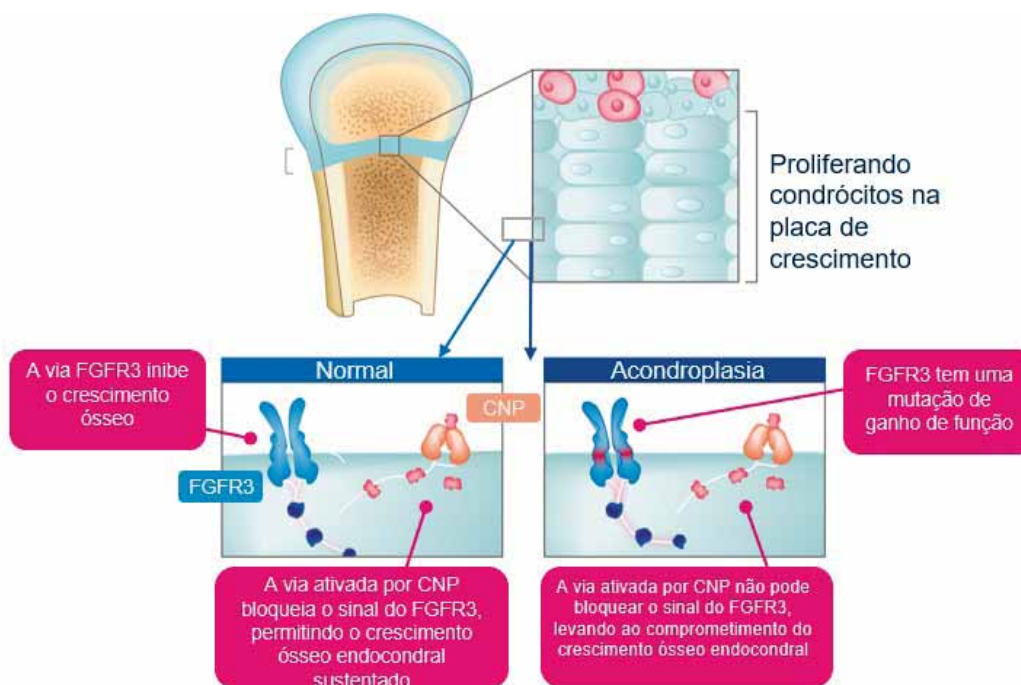
A acondroplasia é causada por mutações de ganho de função no gene FGFR3, que codifica o receptor 3 do fator de crescimento de fibroblastos [1, 8-10, 12]. Esse receptor regula negativamente a ossificação endocondral, processo essencial para o crescimento de ossos longos, costelas e vértebras [8, 9, 39].

Em condições normais, há equilíbrio entre a sinalização do FGFR3 e do peptídeo natriurético tipo C (CNP), que promove o crescimento ósseo ao inibir a via MAPK [8, 9, 39]. Na acondroplasia, a mutação leva à ativação persistente do FGFR3, resultando em bloqueio da ossificação endocondral e baixa estatura desproporcional [10, 11, 50].

Genética e herança:

- 80% dos casos decorrem de mutações espontâneas (de novo); 20% são herdados de um dos pais afetados [51].
- O risco de mutação espontânea aumenta com a idade paterna; pais  $\geq 35$  anos têm risco 3,5 vezes maior [51, 52].
- Em ~90% dos casos, a mutação ocorre no nucleotídeo 1138 do FGFR3; os demais envolvem outras mutações pontuais (p.ex., c.1620C>A/G) [10, 53].

**Figura 1. Ossificação endocondral com *FGFR3* normal versus *FGFR3* mutado (com acondroplasia)**



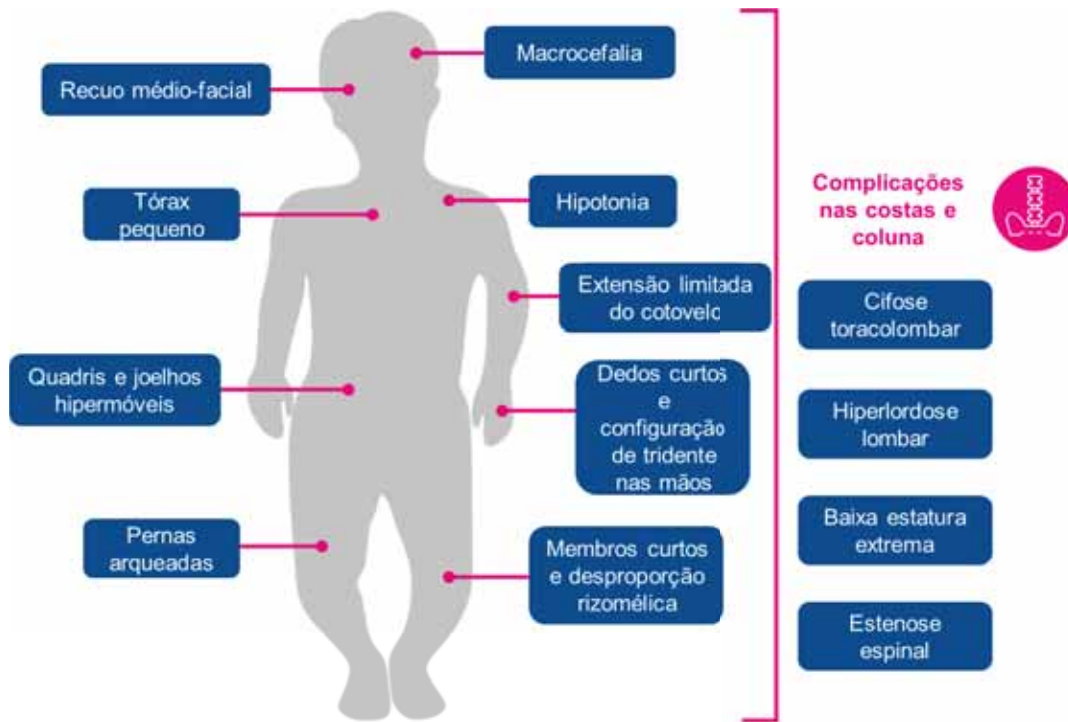
Abreviações: CNP: Peptídeo natriurético tipo C. *FGFR3*: receptor 3 do fator de crescimento de fibroblasto. Fonte: Adaptado de Ornitz and Legeai-Mallet (2017) [50].

## 1.2 Características clínicas da acondroplasia

A acondroplasia é uma doença complexa e multissistêmica, cujas manifestações começam no nascimento e evoluem ao longo da vida [1, 11, 12, 49]. O comprometimento da ossificação endocondral leva a alterações estruturais marcantes e a uma série de complicações que impactam funcionalidade, qualidade de vida e sobrevivência. Embora a baixa estatura desproporcional seja a característica mais visível, a condição envolve múltiplos sistemas, exigindo abordagem além do manejo sintomático.

As características clínicas associadas à acondroplasia são resumidas na [Figura 2](#) e na [Tabela 25 \(no ANEXO II\)](#).

**Figura 2. Visão geral das características clínicas da acondroplasia**



Fonte: Pauli (2019) [1].

### 1.2.1 Baixa estatura desproporcional

A baixa estatura desproporcional é a manifestação clínica mais evidente da acondroplasia. A altura final média é de 124 cm para mulheres e 131 cm para homens, com escore Z entre -5 e -7 [42-45]. O déficit é precoce e concentrado nos primeiros anos: em meninos, cerca de 33% da perda total ocorre até os 2 anos e 51% até os 5 anos; em meninas, 37% e 59%, respectivamente [13]. O crescimento pós-natal pode parecer normal nos primeiros meses, mas a taxa cai abruptamente após esse período, sem pico puberal significativo [13, 15, 54, 55]. Em comparação à população geral, há perda acumulada de aproximadamente 15 cm até os 2 anos e 23 cm até os 5 anos [19]. Esses dados reforçam que a baixa estatura é grave, precoce e progressiva.

Além da estatura reduzida, a acondroplasia apresenta desproporcionalidade marcante entre tronco e membros. O tronco mantém comprimento próximo ao normal, enquanto ossos longos apresentam encurtamento acentuado (rizomelia), resultando em membros curtos e alcance limitado [55]. Em adultos, a envergadura média é de 122 cm para



homens e 110 cm para mulheres, contra 186 cm e 174 cm na população geral no mundo [55]. Essa discrepância compromete atividades cotidianas e independência funcional. Outras alterações incluem macrocefalia progressiva, recuo médio-facial, tórax pequeno, cifose toracolombar, hiperlordose lombar, extensão limitada de cotovelos, mãos em tridente, quadris e joelhos hipermóveis e hipotonia [1, 16, 55, 56]. A macrocefalia, por exemplo, pode atingir +3 desvios padrão aos 2 anos, sendo frequentemente acompanhada por hidrocefalia [55].

### 1.2.2 Sintomas e complicações da acondroplasia

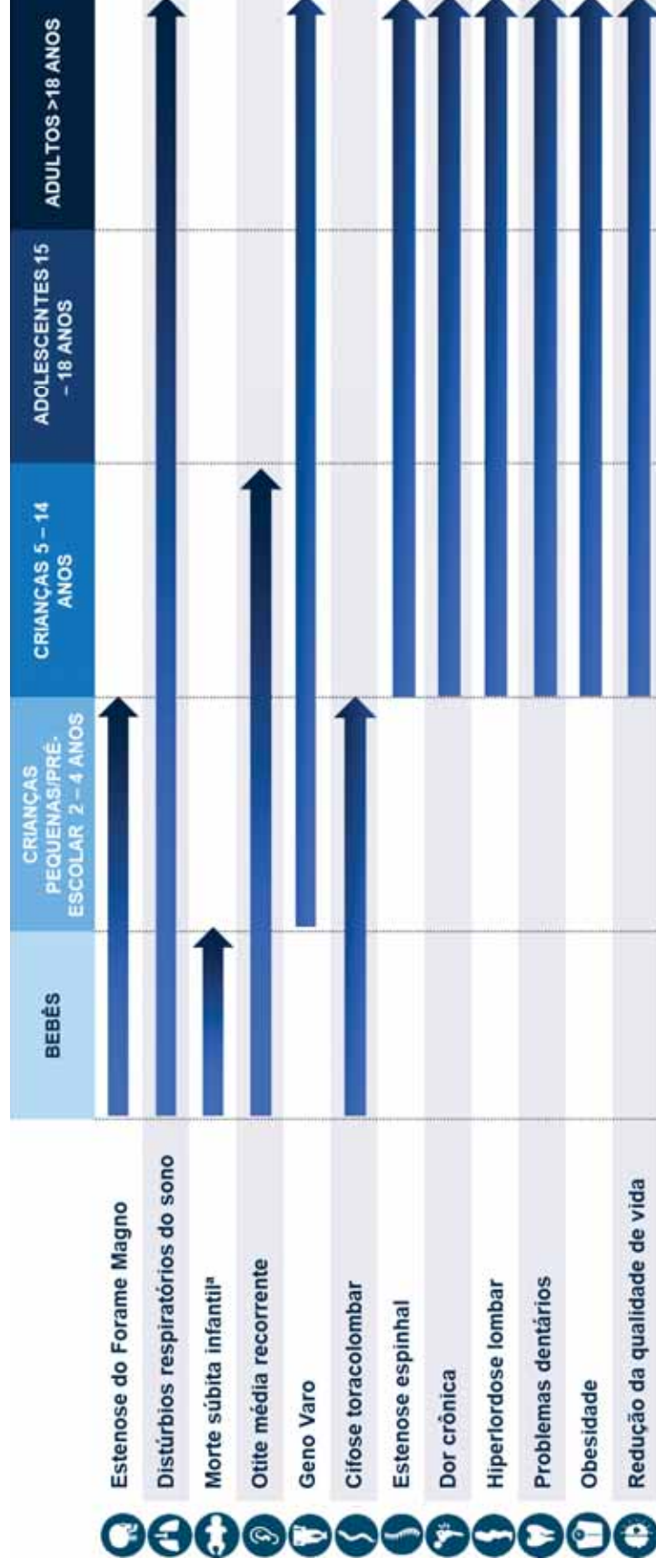
A acondroplasia não se limita ao fenótipo esquelético e não se restringe à infância. O crescimento ósseo prejudicado durante os primeiros anos de vida se acumula até que as epífises se fundam e a altura adulta final seja alcançada, levando a complicações multissistêmicas potencialmente graves que podem afetar o desenvolvimento e se manifestar como desafios funcionais ao longo da vida, incluindo complicações neurológicas, respiratórias, auditivas, ortopédicas e metabólicas.

Entre os problemas neurológicos, destaca-se a estenose do forame magno, que pode causar compressão cervicomedular, hidrocefalia e risco de morte súbita (até 7,5% no primeiro ano) [1, 57]. Distúrbios respiratórios são frequentes, incluindo apneia obstrutiva do sono (presente em até 54% das crianças) e obstrução de vias aéreas superiores, muitas vezes exigindo cirurgias como adenoidectomia e tonsilectomia [1, 18]. Otite média recorrente afeta cerca de 90% das crianças antes dos 2 anos, podendo evoluir para perda auditiva (25% até a adolescência) e atraso de fala [58, 59]. Alterações dentárias, como má oclusão e mordida cruzada, são comuns [18, 60].

Com o avanço da idade, surgem ou se agravam complicações ortopédicas (genu varo, estenose espinhal, contraturas, osteoporose), dor crônica (presente em até 75% dos adultos) e redução da mobilidade [1, 11, 18-20, 49, 59, 61]. A obesidade, que pode atingir 10% dos pacientes antes dos 18 anos, agrava problemas ortopédicos e respiratórios [62-64]. Em adultos, a prevalência de doenças cardiovasculares é elevada, com risco de morte por causas cardíacas até 10 vezes maior que na população geral [2, 17, 65]. Esses dados reforçam que a acondroplasia é uma condição de alta complexidade clínica, com impacto cumulativo ao longo da vida.

Os sintomas comumente observados e complicações estratificadas pela idade em que afetam os pacientes com acondroplasia são apresentados na [Figura 3](#).

Figura 3. Início de complicações secundárias comuns de acondroplasia por faixa etária



<sup>a</sup>6x maior do que a população em geral (Simmons K et al.; Birth Defects Res A Clin Mol Teratol. 2014, [56]), impactando ~ 2% das crianças pequenas com acondroplasia (Armstrong JA et al. Dev Med Child Neurol. [66])  
Referências [10, 12, 57, 67]

### ***Bebês (0 até <2 anos)***

O período inicial é crítico devido ao risco neurológico. A estenose do forame magno é a complicação mais grave, podendo causar compressão cervicomedular, hidrocefalia e morte súbita, com taxas de até 7,5% no primeiro ano [1, 57]. Essa compressão também contribui para apneia do sono, presente em cerca de 67% dos bebês [68]. Em aproximadamente 10% dos casos, é necessária cirurgia descompressiva para reduzir o risco de óbito [1]. Além disso, há alta incidência de otite média (90% antes dos 2 anos), frequentemente exigindo colocação de tubos de timpanostomia [55, 69]. Atrasos motores e de comunicação são comuns, associados à hipotonia [1, 70].

### ***Crianças pequenas / pré-escolar (2 até 4 anos)***

Embora o risco de morte súbita diminua, complicações respiratórias persistem. Apneia obstrutiva do sono e obstrução das vias aéreas superiores continuam frequentes, muitas vezes exigindo cirurgias como adenoidectomia ou tonsilectomia [40]. Alterações auditivas e de fala tornam-se mais evidentes: cerca de 20% apresentam atraso na aquisição da fala, relacionado à disfunção da tuba auditiva [67]. Nesse período, surgem deformidades ortopédicas marcantes, como genu varo, observado em até 40% das crianças, com progressão rápida entre 3 e 4 anos [60, 62].

### ***Crianças (5–14 anos)***

As complicações respiratórias permanecem relevantes, com apneia obstrutiva do sono em até 54% dos pacientes, exigindo manejo contínuo [63]. Alterações da coluna, como cifose toracolombar e hiperlordose lombar, podem persistir ou exigir intervenção [1, 71]. Problemas ortodônticos, como má oclusão e mordida cruzada, tornam-se mais pronunciados, afetando mais da metade dos pacientes [67, 71]. A obesidade surge como fator adicional, afetando cerca de 10% dos menores de 18 anos, agravando complicações ortopédicas e respiratórias [57, 58, 64].

### ***Adolescentes (15-18 anos)***

Complicações crônicas se consolidam. A dor musculoesquelética é frequente, afetando até 23% dos adolescentes [40]. A estenose espinhal sintomática pode surgir nessa fase, atingindo até 20% dos pacientes [1, 20]. A perda auditiva, consequência de otites recorrentes, é relatada em cerca de 25% antes dos 18 anos [59, 67]. Esses fatores impactam mobilidade, desempenho escolar e qualidade de vida.

### **Adultos (> 18 anos)**

Na vida adulta, as complicações atingem seu pico. A dor crônica afeta entre 64% e 75% dos pacientes, associada à estenose espinhal, que pode atingir 80% aos 60 anos [20, 67, 72]. A mobilidade é severamente comprometida, levando à dependência funcional. Além disso, há alta prevalência de doenças cardiovasculares (até 56%), com risco de morte por causas cardíacas até 10 vezes maior que na população geral [22, 57]. A obesidade e a limitação para atividade física agravam esse cenário [1].

### **1.3 Impacto na qualidade de vida e funcionalidade do paciente com acondroplasia**

As consequências da acondroplasia, principalmente a baixa estatura desproporcional e as múltiplas complicações, afetam negativamente a qualidade de vida (QV) em diversos domínios — físico, social, emocional e profissional — ao longo de toda a vida [23, 24]. Estudos mostram que indivíduos com acondroplasia apresentam escores significativamente mais baixos no questionário “Qualidade de Vida em Jovens de Baixa Estatura” (QoLISSY) ( $p < 0,001$ ), especialmente nos domínios físico e social, quando comparados a pessoas com baixa estatura proporcional [57]. Além disso, muitos pacientes não conseguem realizar atividades básicas de forma independente, conforme evidenciado em estudos com instrumentos específicos e genéricos de QV abaixo (*Tabela 1*) [4, 5, 21, 23-25, 28, 29, 73, 74].

É importante considerar o chamado “paradoxo da deficiência”, pelo qual pacientes podem subestimar o impacto da doença por nunca terem vivido sem ela [27]. Um estudo de “Experiência de Escolha Discreta / Permuta com o Tempo” (DCE/TTO) com pessoas com acondroplasia mostrou diferença média de +0,06 vs. o conjunto de valores US EQ-5D-5L e utilidades maiores em 67% dos 3.125 estados do EQ-5D-5L, o que indica potencial subestimação do impacto quando se utilizam valores da população geral [75].

**Tabela 1. Atividades de vida diária prejudicadas entre pacientes com acondroplasia dos EUA**

ATIVIDADE	PACIENTES ADULTOS COM ACONDROPLASIA RELATANDO PERDA DE CAPACIDADE
Tomar banho e vestir-se independentemente	10,7%
Usar o banheiro independentemente	11,3%
Fazer compras	16,4%
Cozinhar/ fazer trabalhos domésticos	15,7%



Andar	2,6%
Subir um lance de escadas sem ajuda	14,7%
Caminhar por longas distâncias *	33,3%

\* Capaz de andar pela comunidade.

Abreviações: EUA: Estados Unidos da América.

Fonte: Alade et al (2013) [4]

### 1.3.1 Funcionamento físico e mobilidade

A baixa estatura e a desproporcionalidade reduzem significativamente a mobilidade e o alcance funcional. Pacientes apresentam escores físicos inferiores aos de indivíduos não afetados, com impacto maior em mulheres e idosos [21, 25]. Limitações anatômicas, como membros curtos e restrição articular, dificultam atividades de autocuidado (vestir-se, tomar banho, usar o banheiro), podendo gerar problemas de higiene [4, 76]. Além disso, complicações ortopédicas — contraturas, estenose espinhal, genu varo — e dor crônica aumentam a dificuldade para caminhar ou subir escadas, levando muitos a depender de dispositivos auxiliares [4, 5, 21]. A dor tende a se intensificar com a idade [1, 4, 12]. Restrições físicas também limitam a capacidade de dirigir, exigindo adaptações específicas.

### 1.3.2 Função social e emocional

As barreiras sociais são uma das principais causas de redução da QV. Pacientes frequentemente enfrentam estigma, isolamento e dificuldades para estabelecer relações interpessoais e afetivas [5, 21, 25, 77]. O impacto psicológico é significativo: baixa autoestima, depressão e ansiedade são comuns, assim como risco aumentado de ideação suicida [25, 74]. A dor crônica, presente desde a adolescência, contribui para o sofrimento emocional e piora a percepção de bem-estar [21]. Esses fatores reforçam a necessidade de suporte psicossocial contínuo.

### 1.3.3 Relação entre altura e qualidade de vida

Diversos estudos demonstram correlação direta entre altura e QV em pacientes com acondroplasia e outras displasias esqueléticas [6, 24, 78]. Maior estatura está associada a melhor funcionalidade e independência, achado também observado na população geral [79]. Dados do estudo 111-901 (n=121; 4–15 anos) indicam que o escore Z de altura prediz QVRS global e funcionamento físico, com relação linear clara entre altura e domínios do questionário *Inventário Pediátrico de Qualidade de Vida* (PedsQL) [63]. Indivíduos com maior déficit ( $\leq -6$  pontuações de desvio padrão (DP)) apresentaram



piores escores em comparação aos com déficit menor ( $> -4$  DP), reforçando que ganhos de crescimento podem gerar benefícios clínicos e psicossociais duradouros.

### **1.3.4 Quantificação da carga da doença e do impacto na qualidade de vida: Os estudos LISA e LIAISE**

O estudo latino-americano *Lifetime Impact Study for Achondroplasia* (LISA) [80] foi um estudo observacional, multinacional e retrospectivo, com componente transversal, realizado entre 2018 e 2021 em quatro centros de Argentina, Brasil e Colômbia, incluindo 172 participantes com diagnóstico de acondroplasia, dos quais 94 brasileiros. A metodologia envolveu aplicação de questionários validados para avaliação da qualidade de vida relacionada à saúde, incluindo QoLISSY, PedsQL e *EuroQol 5 Dimensions* (EQ-5D-5L), além de coleta de dados clínicos e de uso de recursos médicos a partir de prontuários. Os participantes foram estratificados por faixa etária e país, e os dados analisados por meio de estatística descritiva, permitindo comparação com populações de estatura média e entre países.

Os resultados do LISA evidenciam que a acondroplasia impõe significativa redução da qualidade de vida em todas as idades, com maior impacto nos domínios físico e social, conforme demonstrado pelas escalas QoLISSY e PedsQL. Mais de 50% dos adolescentes relataram dor em pelo menos um local, e 10% dos adultos referiram dor em três ou mais sítios, sendo dor, mobilidade e energia os principais problemas identificados no questionário *Nottingham Health Profile* (NHP). Adultos apresentaram taxas elevadas de ansiedade/depressão (26,6%) e dificuldades de mobilidade (20,3%) no EQ-5D-5L. O estudo também revelou alta frequência de eventos médicos, especialmente distúrbios musculoesqueléticos, otorrinolaringológicos e infecções, resultando em elevado uso de recursos de saúde, como consultas, exames e cirurgias. Esses dados, obtidos em contexto latino-americano e brasileiro, reforçam o impacto persistente da doença e a necessidade de intervenções que promovam crescimento, funcionalidade e bem-estar.

O estudo europeu LIAISE (n=186) confirma que a acondroplasia reduz QV em todas as idades, com maior impacto nos domínios físico e de enfrentamento [81]. Em crianças, as escalas QoLISSY e PedsQL mostram comprometimento significativo, enquanto em adultos, o EQ-5D-5L revela problemas moderados a graves relacionados à dor (38%) e mobilidade (18%) [81]. Esses dados evidenciam que a doença impõe limitações



persistentes, justificando intervenções que melhorem crescimento, funcionalidade e bem-estar.

## **1.4 Impacto societário da acondroplasia**

A acondroplasia não afeta apenas o indivíduo, mas também sua inserção social, educacional e profissional, além de impactar significativamente a vida familiar e os cuidadores [28-30, 67, 77, 78, 82-84].

### **1.4.1 Adesão e desempenho escolar**

Crianças e adolescentes com acondroplasia apresentam desempenho escolar inferior em comparação a pares não afetados [28, 77]. Barreiras auditivas e de fala prejudicam a comunicação em sala de aula, enquanto limitações de mobilidade e estigma social dificultam a participação em atividades escolares [28, 67, 82, 83]. A fadiga após curtos períodos de escrita, devido à restrição articular e dor, é comum [83]. Intervenções ambientais e comportamentais são frequentemente necessárias. Dados do estudo LIAISE indicam correlação positiva entre escore Z de altura e domínio escolar do PedsQL, sugerindo que ganhos de crescimento podem melhorar o desempenho educacional.

### **1.4.2 Empregabilidade e produtividade**

Adultos com acondroplasia enfrentam menor taxa de empregabilidade e opções de carreira restritas [28]. Limitações físicas dificultam atividades que exigem esforço ou operação de máquinas, enquanto trabalhos sedentários podem agravar dor crônica, exigindo adaptações [73]. Ausências frequentes por complicações médicas reduzem produtividade e aumentam risco de desemprego.

### **1.4.3 Impacto na vida familiar e dos cuidadores**

O diagnóstico de acondroplasia impõe carga física e emocional significativa aos cuidadores, que relatam sentimentos de choque, tristeza e ansiedade [23, 30, 84]. A rotina familiar sofre alterações, com restrições em viagens, lazer e atividades sociais [84]. Irmãos não afetados podem assumir responsabilidades adicionais e receber menos atenção [84]. Esses fatores contribuem para redução da qualidade de vida familiar.

#### **1.4.4 Caracterização como deficiência**

No Brasil, o nanismo é reconhecido como deficiência física desde 2004 (Decreto 5.296/04), reforçado pela Lei 549/22. Assim, indivíduos com acondroplasia estão incluídos na Política Nacional de Atenção Integral à Saúde da Pessoa com Deficiência (PNAISPD), garantindo direitos e acesso a políticas públicas.

#### **1.5 Impacto econômico da acondroplasia**

O ônus econômico da acondroplasia é elevado, abrangendo custos diretos e indiretos. Desde a infância, pacientes utilizam mais recursos de saúde do que a população geral, incluindo consultas frequentes, fisioterapia, fonoaudiologia (10% a 47% dos pacientes), cirurgias ortopédicas e neurológicas, internações e uso contínuo de medicamentos [67, 71, 73, 78].

Os custos indiretos incluem perda de produtividade de pacientes e cuidadores, absenteísmo escolar e laboral e necessidade de adaptações domiciliares [28, 73, 78]. O tempo dedicado a tratamentos representa um custo de oportunidade significativo, impactando renda familiar e participação social [84].

Nos EUA, análise de 1.985 internações em 2017 estimou custo hospitalar de US\$ 40 milhões apenas para esse ano [31]. No Brasil, não há estudos robustos, mas a subutilização do CID específico e o manejo predominantemente sintomático sugerem subnotificação dos custos reais [32].

#### **1.6 Risco de mortalidade**

Pacientes com acondroplasia apresentam risco elevado de mortalidade, especialmente nos primeiros anos de vida, e expectativa de vida reduzida em cerca de 10 anos em relação à população geral [1, 57, 58]. A morte súbita é uma preocupação importante na infância: bebês têm risco 3 a 6 vezes maior de óbito, podendo chegar a 7,5% no primeiro ano e 2,5% entre 1 e 4 anos [53]. A principal causa é a estenose do forame magno, que leva à compressão cervicomedular [1].

Na vida adulta, a mortalidade continua elevada, principalmente por doenças cardiovasculares, que representam a principal causa de morte. O risco de óbito por causas cardíacas pode ser 10 vezes maior entre 25 e 35 anos em comparação à



população geral [22]. Esses dados reforçam a gravidade da doença e a necessidade de manejo além do tratamento sintomático.

## 1.7 Epidemiologia da acondroplasia

A acondroplasia é uma doença rara multissistêmica, progressiva e crônica, tipicamente reconhecida por ser a forma mais comum de baixa estatura desproporcional, com incidência global estimada em 1 a cada 25.000–30.000 nascidos vivos e cerca de 250.000 pessoas afetadas no mundo [1, 10]. Uma metanálise recente estimou prevalência média global de 4,6 por 100.000 nascimentos (IC 95%: 3,9–5,4) [3]. Na América do Sul, a prevalência é de 3,2 por 100.000, e no Brasil estima-se aproximadamente 7.600 pessoas com acondroplasia [3, 32, 33, 51, 85]. As estimativas regionais de prevalência de nascimentos na acondroplasia são apresentadas na [Tabela 26, no ANEXO II](#).

## 1.8 Diagnóstico da acondroplasia

O diagnóstico geralmente é realizado na primeira infância, com base em características clínicas e exames radiográficos [86]. A confirmação molecular é recomendada para diferenciar de outras displasias [87]. O diagnóstico pré-natal é possível por ultrassonografia no terceiro trimestre e testes genéticos invasivos (amniocentese, biópsia de vilos coriais) [1, 88, 89]. Testes não invasivos com DNA fetal livre também são viáveis, mas não estão disponíveis no SUS [88, 90].

As diretrizes da *American Academy of Pediatrics* e da Sociedade Brasileira de Pediatria reforçam a importância da confirmação molecular e do monitoramento precoce de complicações, como estreitamento do forame magno [1].

[Tabela 30, no ANEXO II](#), apresenta detalhes sobre o que recomendação da *American Academy of Pediatrics* e Sociedade Brasileira de Pediatria para o diagnóstico de acondroplasia.

## 1.9 Tratamentos atuais

Historicamente, o manejo da acondroplasia no Brasil e no mundo foi restrito ao tratamento sintomático, sem atuar na causa subjacente [1, 12, 34]. O cuidado envolve múltiplos procedimentos invasivos, uso de medicamentos para controle de sintomas, intervenções ambientais e acompanhamento multidisciplinar contínuo [37, 61, 91-95].



Não existe PCDT específico no SUS, resultando em cuidados fragmentados e paliativos [92].

### **1.9.1 Carga cirúrgica e impacto do manejo sintomático**

A maioria dos pacientes é submetida a múltiplas cirurgias ao longo da vida (ver Figura 4), incluindo:

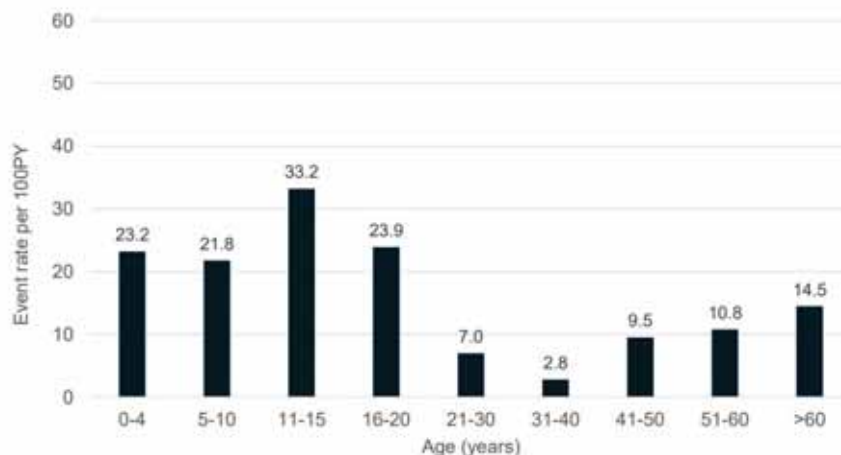
- Descompressão cervicomedular: necessária em 5–41% das crianças para tratar estenose do forame magno e prevenir morte súbita [61, 91-95].
- Cirurgias otorrinolaringológicas: adenoidectomia, amigdalectomia e timpanostomia para tratar otite média e obstrução das vias aéreas [18, 58, 91].
- Cirurgias ortopédicas: correção de geno varo, osteotomias e artrodeses [35, 37, 96-102].
- Alongamento ósseo: procedimento invasivo, prolongado e doloroso, com risco de infecção, fraturas e complicações articulares. Apesar de aumentar a altura (média 5,7–20,5 cm), não altera a história natural da doença e pode reduzir a velocidade de crescimento [36, 93-95, 103].

Além das cirurgias, pacientes utilizam analgésicos, opioides, antibióticos, anti-inflamatórios e tratamentos para complicações respiratórias e metabólicas [27, 91, 104].

Esse manejo fragmentado gera alto ônus físico, emocional e financeiro:

- 79,6% dos pacientes já passaram por pelo menos uma cirurgia [34].
- Uso intensivo de recursos de saúde (fisioterapia, fonoaudiologia, exames frequentes) [27, 32, 81].
- Perda de produtividade e sobrecarga emocional para pacientes e cuidadores [27, 28, 33, 81].

**Figura 4. Incidência de procedimentos cirúrgicos por faixa etária (eventos por 100 indivíduos) Adaptado de: CLARITY/Achondroplasia Natural History [34]**



Devido à ausência de tratamento que enderece a causa subjacente da acondroplasia, há interesse acadêmico sobre a possível utilização de hormônio do crescimento (GH). No entanto, o GH não é recomendado para acondroplasia, pois, uma vez que não há deficiência endógena, ele não endereça a causa subjacente da doença [104-108]. Estudos mostram aumento limitado e não sustentado da altura, sem impacto funcional relevante ou benefício em redução de desproporcionalidade [104-109]. Além disso, há risco de efeitos adversos, como progressão de escoliose, hipertensão intracraniana, artralgia e até neoplasias secundárias [104, 110-115]. O Ministério da Saúde contraindica o uso de GH em displasias esqueléticas [104].

### 1.9.2 Necessidades médicas não atendidas

Pessoas com acondroplasia e seus cuidadores valorizam tratamentos que facilitam o alcance de objetivos individuais, incluindo ganhos de altura e proporcionalidade corporal que possibilitem atividades diárias, reduzam complicações e melhorem o funcionamento físico e social.

Apesar dos avanços no diagnóstico, persiste uma necessidade substancial de um tratamento farmacológico eficaz, seguro e bem tolerado que atue na causa da doença [1, 12, 34, 38, 116]. As principais lacunas incluem:

- Falta de terapia que aborde a causa subjacente da doença, melhorando o crescimento ósseo e a proporcionalidade corporal, permitindo a realização de atividades diárias, reduzindo complicações que afetam o desenvolvimento causam desafios funcionais ao longo da vida.



- Impacto negativo na qualidade de vida, principalmente nos domínios sociais, emocionais e funcionais.
- Impacto negativo na inclusão social e profissional.
- Elevado ônus econômico e emocional para famílias e sistema de saúde [27, 32, 63, 65, 71, 81].

### **1.9.3 Diretriz brasileira (Sociedade Brasileira de Pediatria)**

A Sociedade Brasileira de Pediatria (SBP) reconhece a vosoritida como o único tratamento farmacológico aprovado que atua na fisiopatologia da acondroplasia, recomendando seu uso precoce com acompanhamento multidisciplinar [38, 116]. A diretriz também orienta:

- Encaminhamento precoce para centros especializados.
- Educação e consentimento informado.
- Monitoramento rigoroso do crescimento, desenvolvimento e efeitos adversos.
- Interrupção do tratamento quando as epífises se fecharem ou não houver benefício clínico.

Além da vosoritida, a SBP lista cuidados complementares, como analgesia, fisioterapia, orientação nutricional, prevenção de obesidade e suporte psicossocial.

A Tabela 28, no ANEXO II, traz um resumo dos tratamentos e cuidados médicos indicados pela Sociedade Brasileira de Pediatria no tratamento da acondroplasia

### **1.9.4 Diretriz internacional sobre o uso de vosoritida**

O consenso internacional publicado em 2025 reforça a importância do início precoce da vosoritida, definição de metas individualizadas e monitoramento contínuo [117]. O desenvolvimento da diretriz contou com a participação de 14 especialistas clínicos de diversos países, incluindo um especialista brasileiro. As recomendações incluem:

- Triagem e encaminhamento imediato para centros especializados.
- Educação e gestão de expectativas com pacientes e cuidadores.



- Treinamento para administração domiciliar e supervisão da primeira dose.
- Monitoramento regular (crescimento, efeitos adversos, adesão).
- Plano de transição após fechamento das epífises.

Presentes no ANEXO II, a Tabela 29 apresenta as etapas práticas e considerações para iniciar e monitorar o tratamento com vosoritida e a Tabela 30 apresenta uma lista de recomendações para o seu monitoramento.



## 2. DESCRIÇÃO DA TECNOLOGIA PROPOSTA

VOXZOGO® (vosoritida) é aprovado para o tratamento da acondroplasia em pacientes a partir de 6 meses de idade, com epífises abertas e diagnóstico confirmado por teste genético [127]. O teste genético confirmatório é fornecido pela BioMarin, através de seu Programa de Suporte ao Paciente (PSP). A administração é subcutânea diária, realizada em ambiente domiciliar por cuidador treinado.

### 2.1 Mecanismo de ação

Vosoritida é um análogo modificado do peptídeo natriurético tipo C (CNP). Em pacientes com acondroplasia, a mutação no FGFR3 hiperativa a via MAPK, inibindo a ossificação endocondral. A vosoritida liga-se ao receptor NPR-B, aumentando cGMP e antagonizando a sinalização do FGFR3, o que reduz a atividade da via ERK1/2 e restaura a proliferação e diferenciação dos condrócitos [127]. Assim, atua diretamente na fisiopatologia da doença, promovendo crescimento ósseo endocondral.

### 2.2 Farmacodinâmica

O tratamento com vosoritida aumenta biomarcadores de atividade óssea:

- cGMP urinário (atividade do NPR-B) eleva-se nas primeiras 4 horas pós-dose.
- CXM sérico (formação óssea endocondral) aumenta até o 29º dia e mantém-se por mais de 24 meses [127].

As doses em bula de 15-30 mcg/kg/dia atingem saturação da atividade do NPR-B e efeito máximo na placa de crescimento [127].

### 2.3 Farmacocinética

Vosoritida é um peptídeo recombinante derivado de CNP humano, com duas modificações que conferem resistência à degradação e meia-vida prolongada [116]. Estudos em crianças de 2 a 18 anos demonstraram perfis farmacocinéticos semelhantes, com administração subcutânea diária [116].

### 2.4 Contraindicações

Hipersensibilidade ao princípio ativo ou a qualquer excipiente da formulação [104, 116].

## 2.5 Posologia

O tratamento deve iniciar o mais cedo possível para maximizar benefícios [116]. A dose recomendada varia entre 15 mcg/kg/dia s e 30 mcg/kg/dia, ajustada pelo peso corporal. Abaixo, a Tabela 2 apresenta os volumes correspondentes:

**Tabela 2. Volume de dose única por peso corporal [116]**

Peso corporal (Kg)	VOXZOGO® (vosoritida) 0,4 mg Diluyente (água para injetáveis): 0,5 mL Concentração: 0,8 mg/mL	VOXZOGO® (vosoritida) 0,56 mg Diluyente (água para injetáveis): 0,7 mL Concentração: 0,8 mg/mL	VOXZOGO® (vosoritida) 1,2 mg Diluyente (água para injetáveis): 0,6 mL Concentração: 2 mg/mL
	Volume de injeção diária (ml)		
5	0,20 ml		
6-7	0,25 ml		
8-11	0,30 ml		
12-16		0,35 ml	
17-21		0,40 ml	
22-32		0,50 ml	
33-43			0,25 ml
44-59			0,30 ml
60-89			0,35 ml
≥90			0,40 ml

Orientações adicionais:

- Interromper o tratamento quando a velocidade de crescimento for <1,5 cm/ano e houver fechamento das epífises [116].
- Se uma dose for esquecida, pode ser administrada em até 12 horas; após esse período, deve ser pulada [116].
- Monitoramento a cada 3–6 meses para ajuste de dose conforme peso e avaliação do crescimento [116].

### 3. REVISÃO SISTEMÁTICA DA LITERATURA (RSL)

A Revisão Sistemática da Literatura RSL foi conduzida para avaliar a eficácia e segurança da vosoritida no tratamento da acondroplasia em pacientes a partir de 6 meses de idade e cujas epífises não estão fechadas. Foram incluídos ensaios clínicos de fase II e III, estudos de vida real e revisões sistemáticas com ou sem meta-análise, comparando vosoritida a placebo ou controle histórico [consulte a Pergunta PICO na Tabela 3].

A busca estruturada nas bases PUBMED, EMBASE e Cochrane Library identificou 235 referências, das quais 7 publicações foram incluídas na análise final: 4 do estudo fase III 111-301/302, 1 do estudo fase II 111-202, 1 do estudo fase II 111-206 e 1 estudo de vida real.

#### 3.1 Métodos

##### 3.1.1 Objetivo

O objetivo desta revisão sistemática é avaliar a eficácia e segurança do uso de vosoritida no tratamento da acondroplasia, a fim de fornecer uma análise abrangente e fundamentada dos resultados clínicos obtidos.

##### 3.1.2 Questão de pesquisa

A questão de pesquisa foi estruturada no formato PICO ([Tabela 3](#)).

**Tabela 3. Questão estruturada no formato PICO.**

<b>P - População</b>	Pacientes com acondroplasia a partir de 6 meses de idade e cujas epífises não estão fechadas
<b>I – Intervenção</b>	Vosoritida
<b>C – Comparação</b>	Placebo
<b>O – Desfechos</b>	Eficácia: Mudança na altura, velocidade de crescimento, Relação segmento superior:segmento inferior do corpo, ou outras proporções corporais, Escore Z de altura, Altura final adulta, Segurança: Eventos adversos, descontinuação, óbitos Qualidade de vida relacionada à saúde
<b>Desenho de Estudo</b>	Revisões sistemáticas com ou sem meta-análise e ensaios clínicos fase II e/ou III ou estudos de vida real



**Pergunta:** Vosoritida é eficaz e segura no tratamento de pacientes com acondroplasia a partir de 6 meses de idade e cujas epífises não estão fechadas quando comparado a placebo?

### 3.1.3 Estratégia de busca

Foi realizada uma busca estruturada nas três bases de dados principais: PUBMED, EMBASE e Cochrane Library em 12 de novembro de 2024 e posteriormente atualizada em 16 de agosto de 2025 utilizando as palavras-chave apresentadas na [Tabela 4](#).

**Tabela 4. Estratégia de busca**

Base de dados	Estratégia de busca	Resultado
PUBMED	("Achondroplasia"[Mesh] OR Achondroplasia) AND ("vosoritide" [Supplementary Concept] OR vosoritide OR BMN 111)	73
EMBASE	('achondroplasia'/exp OR achondroplasia) AND ('vosoritide'/exp OR vosoritide OR 'bmn 111'/exp OR 'bmn 111' OR (bmn AND 111))	220
Cochrane Library	Achondroplasia AND (vosoritide OR BMN 111)	35

### 3.1.4 Critérios de elegibilidade

Foram incluídos artigos na íntegra que atenderam às seguintes características:

- Revisões sistemáticas com ou sem meta-análises, estudos clínicos de fase II e/ou III, estudos prospectivos, estudos de vida real
- Incluindo pacientes com acondroplasia a partir de 6 meses de idade e cujas epífises não estão fechadas
- Em comparação direta ou indireta, através de controle histórico, com placebo

Alguns critérios de exclusão foram estabelecidos: ensaios pré-clínicos (com modelos animais), estudos de fase I, estudos de farmacocinética ou farmacodinâmica, estudos de outros idiomas que não sejam inglês, espanhol e português.

### 3.1.5 Seleção dos estudos

Dois revisores selecionaram os estudos conforme critérios de elegibilidade, primeiramente excluindo estudos duplicados e na sequência através de uma avaliação inicial de título e resumos. Posteriormente, os estudos potenciais selecionados foram analisados com o seu texto na íntegra. Estudos que cumpriram os critérios de



elegibilidade na leitura integral foram incluídos. Em caso de desacordo, um terceiro revisor decidia sobre a inclusão.

### 3.1.6 Coleta dos dados

Os dados como por exemplo desenho e objetivo do estudo, número e principais características dos pacientes, intervenção, comparador e desfechos foram coletados em tabelas no Excel®.

### 3.1.7 Desfechos avaliados

Os desfechos de eficácia avaliados foram:

- Mudança na altura,
- Velocidade de crescimento,
- Relação segmento superior:segmento inferior do corpo, ou outras proporções corporais,
- Escore Z de altura
- Qualidade de vida relacionada à saúde

Ainda foram avaliados desfechos de segurança, como os eventos adversos, quantidade de descontinuação e óbitos.

### 3.1.8 Avaliação da qualidade da evidência

Para a avaliação da qualidade da evidência, foi utilizado o sistema *The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)*. O sistema GRADE fornece uma abordagem sistemática e transparente para avaliar a certeza nas estimativas dos efeitos, facilitando a tomada de decisões clínicas baseadas em evidências robustas.

## 3.2 Resultados

Foram obtidas 328 referências nas bases de dados consultadas. Após a retirada das duplicatas, analisou-se o título e resumo de 243 referências e, posteriormente, texto completo de 67 referências ([Figura 5](#)). Destas, 10 publicações foram incluídas na análise, sendo 4 publicações do estudo fase III 111-301/302, 1 publicação do estudo fase II 111-202, 1 publicação do estudo fase II 111-206, 1 estudo observacional prospectivo e 3 estudos de vida real. Os estudos excluídos estão listados no [ANEXO III](#).

**Figura 5. Fluxograma PRISMA**



Os estudos incluídos nessa análise estão descritos na [Tabela 5](#). Para maior transparência e melhor visualização, a [Figura 6](#) apresenta detalhes do programa clínico. Além disso, no [ANEXO IV](#) (subitem [9.4](#)) há um detalhamento do desenho dos estudos.

O programa clínico de desenvolvimento da vosoritida foi extenso e metodologicamente robusto. Os principais estudos discutidos ao longo deste dossiê são:

- a. **O estudo pivotal de fase III (111-301):** estudo clínico randomizado, duplo-cego de fase III controlado por placebo com objetivo de avaliar a eficácia e segurança da vosoritida na administração subcutânea uma vez ao dia, numa dose de 15,0 µg/kg de peso corporal, em comparação com placebo em crianças com acondroplasia;
- b. **A extensão do estudo de fase III (111-302):** estudo de extensão de braço único do estudo fase III com acompanhamento da eficácia e segurança do tratamento diário contínuo com vosoritida em crianças com acondroplasia;

- c. **Um estudo de fase II em crianças > 5 anos de idade (111-202):** estudo de braço único multinacional e de escalonamento de dose, com o objetivo de avaliar a segurança e o perfil de efeitos colaterais da vosoritida em crianças com acondroplasia, com idades entre 5 e 14 anos;
- d. **A extensão do estudo de fase II > 5 (111-205);**
- e. **Um estudo de fase II em crianças < 5 anos de idade (111-206):** estudo clínico fase II, randomizado, duplo-cego e controlado por placebo, foi realizado em 16 hospitais na Austrália, Japão, Reino Unido e EUA. O objetivo principal do estudo foi avaliar a segurança e a eficácia da vosoritida em crianças com acondroplasia com menos de 60 meses de idade;
- f. **A extensão do estudo de fase II < 5 (111-208);**
- g. **Quatro estudos de mundo real ([Figura 7](#)).**

**Figura 6. Desenho do programa clínico**



Figura 7. Estudos de Mundo Real (RWE) identificados na RSL



Por fim, para facilitar o entendimento dos resultados clínicos dos estudos, foi organizado um breve descritivo dos principais desfechos clínicos avaliados em acondroplasia, disponível no [ANEXO V](#).

**Tabela 5. Descrição dos estudos**

Nome do Estudo	Tipo do Estudo	POPULAÇÃO	GRUPO INTERVENÇÃO (N)	GRUPO CONTROLE (N)	Desfechos
111-202 e fase de extensão (111-205), [40, 118, 119]	Estudo fase II aberto	Crianças de 5 a 14 anos de idade com história clínica documentada e teste genético positivo para acondroplasia (N= 35 crianças)	<p>Vosoritida:</p> <ul style="list-style-type: none"> <li>• Coorte 1: dose matinal diária de 2,5 µg/ kg</li> <li>• Coorte 2: dose matinal diária de 7,5 µg/ kg</li> <li>• Coorte 3: dose matinal diária de 15,0 µg/ kg</li> <li>• Coorte 4: dose matinal diária de 30,0 µg/ kg</li> </ul> <p><i>Após 6 meses, a dose na coorte 1 foi aumentada para 7,5 µg por quilograma e, em seguida, para 15,0 µg por quilograma, e na coorte 2, a dose foi aumentada para 15,0 µg por quilograma; os pacientes das coortes 3 e 4 continuaram a receber suas doses iniciais.</i></p>	Sem comparador	<ul style="list-style-type: none"> <li>- Eventos adversos</li> <li>- VCA</li> <li>- Escore Z de altura</li> <li>- Proporcionalidade de segmento corporal</li> </ul>
111-301 e fase de extensão (111-302) [7, 41, 42, 44, 108, 120-122]	Estudo fase III randomizado controlado	Crianças de 5 a 18 anos de idade com história clínica documentada e teste genético positivo para acondroplasia (N= 124 crianças)	Vosoritida na dose matinal diária de 15,0 µg/ kg (N= 60)	Placebo (N= 61)	<ul style="list-style-type: none"> <li>- VCA</li> <li>- Escore Z de altura</li> <li>- Mudança da linha de base na proporção corporal do segmento superior para inferior</li> <li>- Segurança e tolerabilidade</li> <li>- Qualidade de vida</li> <li>- Proporcionalidade</li> </ul>



111-206 e fase de extensão (111-208) [123-127]	Estudo fase II randomizado controlado	Crianças de 0 a 5 anos de idade com história clínica documentada e teste genético positivo para acondroplasia (N=75 crianças)	Vosoritida na dose matinal diária de 15,0 µg/ kg ou 30 µg/ kg (N= 43)	Placebo (N= 32)	- Segurança e tolerabilidade - Mudança no escore Z da altura em 52 semanas a partir da linha de base - Qualidade de vida
Cormier-Daire et al 2025 [128]	Estudo de vida real	Crianças com idade ≥5 anos com acondroplasia e epífises abertas (N=62)	Vosoritida na dose diária de 15,0 µg/ kg		- Segurança - Altura - Escore Z de altura - VCA Todos os desfechos medidos durante um período de acompanhamento de 12 meses.
Sawamura et al 2025 [129]	Estudo prospectivo centro único	Crianças com acondroplasia com idade ≤15 anos que receberam vosoritida por pelo menos 12 meses (N=17)	Vosoritida na dose diária de 15,0 µg/ kg (N=17)	-	- Altura - Alinhamento espinal medido a partir de radiografias sagitais da coluna e radiografias anteroposteriores dos membros inferiores bilaterais antes da administração de vosoritida e 12 meses após o tratamento.
Reincke et al 2025 [130]	Estudo de vida real	Crianças com acondroplasia que receberam vosoritida por pelo	Vosoritida na dose diária de 15,0 µg/ kg (N=27)	-	- Segurança - Escore Z de altura - Velocidade de crescimento anualizada



Rua et al 2025 [131]	Estudo de vida real	Crianças com diagnóstico genético de acondroplasia que receberam vosoritida por pelo menos 12 meses (N= 34)	Vosoritida na dose diária de 15,0 µg/ kg (N=34)	-	<ul style="list-style-type: none"> <li>- Teste de caminhada de 6 minutos</li> <li>- Índice de massa corporal</li> <li>- Proporção entre os segmentos superior e inferior do corpo</li> <li>- Circunferência de crânio</li> <li>- Qualidade de vida</li> <li>- Todos os desfechos medidos durante um período de acompanhamento de 12 meses.</li> </ul>
					<ul style="list-style-type: none"> <li>- Segurança</li> <li>- Altura</li> <li>- Escore Z de altura</li> <li>- Velocidade de crescimento anualizada</li> <li>- Todos os desfechos medidos durante um período de acompanhamento de 12 meses.</li> </ul>

### 3.2.1.1 Síntese dos dados clínicos

Os pacientes tratados com vosoritida apresentam melhoria na qualidade de vida e no funcionamento diário devido a resultados positivos significativos e sustentados no crescimento e na proporcionalidade óssea, refletindo os benefícios multissistêmicos deste tratamento.

A velocidade de crescimento anualizada (VCA) e o escore Z de altura foram selecionados como desfechos primários por serem medidas objetivas, clinicamente relevantes e diretamente relacionadas à fisiopatologia da acondroplasia. Esses parâmetros permitem quantificação não invasiva, acompanhamento longitudinal e são amplamente aceitos em protocolos internacionais para avaliação de terapias em distúrbios de crescimento. Além disso, refletem o impacto funcional do tratamento e servem como base para modelagem econômica, pois se correlacionam com qualidade de vida, risco de complicações e mortalidade. No entanto, é importante reforçar que o benefício da vosoritida foi comprovado também na proporcionalidade corporal, na qualidade de vida e em redução de complicações e desfechos clínicos.

#### Velocidade de Crescimento Anualizada (VCA) e Altura

- **Estudo 111-301:** Após 52 semanas, a VCA foi significativamente maior no grupo vosoritida (5,96 cm/ano) versus placebo (4,08 cm/ano), diferença média de 1,57 cm/ano (IC 95%: 1,22–1,93;  $p < 0,0001$ ) [15]. O escore Z de altura também melhorou significativamente (diferença média de 0,28; IC 95%: 0,17–0,39;  $p < 0,0001$ ) [Tabela 12].
- **Extensão 111-302:** O efeito foi mantido por até 4 anos, com ganho adicional estimado de 20 cm para meninos e 16 cm para meninas ao longo de 11 anos de tratamento, atingindo velocidades de crescimento anual semelhante à de crianças sem acondroplasia [7, 42, 123].
- **Estudo 111-202/205:** Em crianças  $>5$  anos, aumento sustentado da VCA por até 7 anos, com ganho adicional de altura de 11,03 cm (IC 95%: 8,62–13,45) em relação à história natural [40, 117].
- **Estudo 111-206/208:** Em crianças  $<5$  anos, vosoritida aumentou a VCA em até 2,62 cm/ano (IC 95%: 1,40–3,83) em relação ao controle histórico, com benefício mais pronunciado em quem iniciou antes dos 3 anos [44, 132].



- **Estudos de vida real:** Dados do Brasil, França, Alemanha e Itália confirmam aumento significativo da altura e da VCA, com resultados consistentes aos ensaios clínicos [128-131].

### Proporcionalidade Corporal

- A vosoritida promoveu crescimento proporcional entre tronco e membros, sem piora da desproporcionalidade [40, 42, 44-47, 133].
- A razão segmento superior/inferior melhorou ou permaneceu estável, indicando benefício funcional além do ganho de altura [40, 42, 44-47, 133].
- Além do crescimento linear, houve redução significativa da lordose lombar e melhora do alinhamento dos membros inferiores (genu varo), indicando benefício funcional adicional [129].
- Vosoritida proporcionou ganhos sustentados em proporcionalidade e manutenção da razão envergadura/altura, aproximando a VCA de pacientes tratados da referência de crianças sem acondroplasia após quatro anos de acompanhamento.

### Qualidade de Vida

- **QoLISSY e PedsQL:** Melhora significativa nos domínios físico e social após 3 anos de tratamento, especialmente quando os pacientes atingem um ganho  $\geq 1$  DP no escore Z de altura [21, 25, 134].
- **Estudos de vida real:** Pacientes brasileiros tratados apresentaram melhora em marcos motores, hipotonia, respiração, redução de infecções e impacto positivo na dinâmica familiar [45, 122]. Há também experiências positivas relatadas em estudos de mundo real conduzidos na França, em Portugal e na Alemanha [47, 130, 131].

### Complicações e Desfechos Clínicos

- **Redução de complicações:** Dados sugerem tendência à redução de complicações neurológicas (estenose do forame magno), respiratórias (apneia do sono) e ortopédicas (geno varo, cifose), especialmente com início precoce do tratamento [40, 42, 129, 132, 134].



- **Evidências de imagem:** Aumento do volume facial, seios da face e área do forame magno em crianças tratadas, sugerindo benefício anatômico relevante [42, 123].
- **Desfechos ortopédicos:** Melhora funcional observada no teste de caminhada de 6 minutos após 12 meses, sugerindo impacto positivo na mobilidade [130]. Evidência radiográfica de melhora no alinhamento espinhal e redução do genu varo após 1 ano de tratamento, potencialmente reduzindo risco posterior de deformidades e cirurgias ortopédicas [129].

### Resultados de Segurança

A vosoritida apresenta excelente segurança e tolerabilidade a longo prazo, e o perfil de segurança no mundo real está alinhado com os resultados dos estudos clínicos. Nenhum paciente apresentou eventos adversos graves ou interrompeu o tratamento com vosoritida devido a preocupações com a segurança.

- **Perfil de segurança favorável:** A maioria dos eventos adversos foi leve e transitória, principalmente reações no local da injeção (eritema, dor, inchaço) [7, 40-43].
- **Eventos adversos graves:** Raros e geralmente não relacionados ao medicamento. Não houve aumento de eventos graves em relação ao placebo [40, 42, 43].
- **Imunogenicidade:** Títulos de anticorpos antidrogas foram detectados em até 42% dos pacientes, mas sem impacto clínico relevante ou associação com eventos adversos [40, 42, 43].
- **Adesão e tolerabilidade:** Alta adesão ao tratamento (>97% em estudos de longo prazo), com baixa taxa de descontinuação [42, 45, 47, 128].

### Qualidade da Evidência

- **GRADE:** A qualidade da evidência foi considerada alta para desfechos relacionados à altura (VCA, escore Z de altura) devido a ser considerado o estudo fase III, randomizado, controlado por placebo [Tabela 19].

- **Robustez dos resultados:** O conjunto de evidências é robusto e consistente, com resultados replicados em diferentes populações, faixas etárias e cenários de vida real.

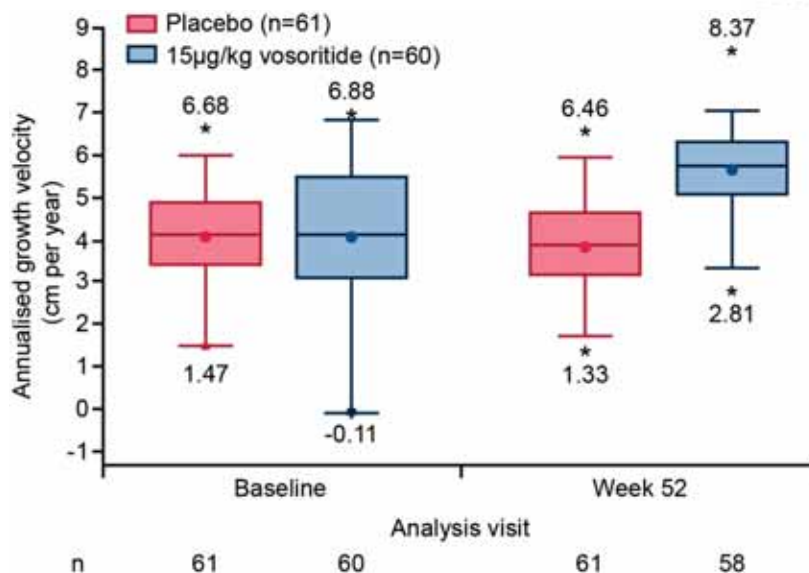
### 3.2.1.2 Estudo fase III com crianças > 5 anos (111-301 e 111-302)

#### *111-301 – Estudo de fase III*

##### **Savarirayan *et al.*, 2020 – estudo pivotal de fase III**

O 111-301 avaliou a eficácia e segurança da vosoritida administrada por via subcutânea, uma vez ao dia, na dose de 15 µg/kg, em comparação ao placebo, em crianças com acondroplasia com mais de 5 anos. As características basais, incluindo a velocidade de crescimento anualizada (VCA) e o escore Z de altura, eram semelhantes entre os grupos antes da intervenção, assegurando comparabilidade clínica. Ao fim de 52 semanas, a vosoritida promoveu um aumento significativo da VCA versus placebo, com restauração substancial do déficit de crescimento característico da acondroplasia; o efeito foi consistente e robusto, sustentado pelas estimativas ajustadas do modelo, com diferença média de aproximadamente 1,57 cm/ano e alta significância estatística (*Figura 8*). O padrão de benefício foi uniforme entre os subgrupos pré-especificados por sexo, idade, estágio puberal e VCA basal, sem evidência de heterogeneidade clinicamente relevante (*Figura 37, no ANEXO II*).

**Figura 8. Velocidade de crescimento anualizada (VCA) na linha de base e 52 semanas por braço de tratamento**



Além do efeito na velocidade, observou-se melhora significativa do escore Z de altura em 52 semanas no grupo vosoritida em comparação ao placebo, com diferença média ajustada de cerca de 0,28 e intervalo de confiança estreito, reforçando relevância clínica e precisão da estimativa. As análises foram conduzidas com médias de mínimos quadrados ajustadas para covariáveis prognósticas (tratamento, sexo, estágio de Tanner, idade e VCA basais), abordagem apropriada para reduzir viés e aumentar a precisão conforme boas práticas (ICH E9), sem alterar a interpretação clínica central dos resultados (*Tabela 6*). A consistência entre subgrupos também se manteve para o escore Z de altura, reforçando a generalização dos achados dentro da população elegível (*Figura 38, no ANEXO II*).

**Tabela 6. Escore Z de altura para pacientes**

	Vosoritida (N=60*)	PLACEBO (N=61)
Linha de base	-5,13 (1,11)	-5,14 (1,07)
Semana 52	-4,89 (1,09)	-5,14 (1,09)
Mudança da linha de base	0,24 (0,32)	0,00 (0,28)
Mudança média LS (IC DE 95%):	0,27 (0,18, 0,36)	-0,01 (-0,10, 0,09)
Diferença média LS na mudança (IC de 95%); valor p	0,28** (0,17, 0,39); p<0,0001***	

\* Dois pacientes do grupo vosoritida descontinuaram o estudo antes da Semana 52. Os valores para estes 2 pacientes foram imputados para esta análise.

\*\* A diferença é de 15 µg/kg de vosoritida menos o placebo. A alteração da linha de base é baseada nos pacientes com medições em ambos os pontos de tempo.

\*\*\* Valor p bilateral.

Abreviações: IC: intervalo de confiança; LS: média dos mínimos quadrado; DP: desvio padrão.



Quanto à proporcionalidade corporal, as razões entre os segmentos superior e inferior do corpo eram semelhantes na linha de base e, após 52 semanas, não houve piora, com estimativas médias praticamente sobreponíveis entre os braços e diferenças não significativas. Em termos clínicos, esse resultado é relevante porque indica que o ganho de crescimento não ocorreu às custas de maior desproporção entre tronco e membros; ao contrário, o padrão observado é compatível com crescimento proporcional, elemento valorizado na avaliação funcional e na expectativa de benefício a longo prazo da terapia.

**Tabela 7. Razão de segmento superior para inferior**

	Vosoritida (N = 60)	PLACEBO (N=61)
Linha de base	1,98 (0,20)	2,01 (0,21)
Semana 52	1,95 (0,20)	1,98 (0,18)
Mudança da linha de base	-0,03 (0,11)	-0,03 (0,09)
Mudança média LS (IC DE 95%):	-0,03 (-0,06, 0,00)	-0,02 (-0,05, 0,01)
Diferença média LS na mudança (IC de 95%); valor p	-0,01* (-0,05, 0,02); p=0,5060**	

\* A diferença é de 15 µg/ kg de vosoritida menos o placebo. A alteração da linha de base é baseada nos pacientes com medições em ambos os pontos de tempo.

\*\* Valor p bilateral.

Abreviações: IC: intervalo de confiança; LS: média dos mínimos quadrados; DP: desvio padrão.

O perfil de segurança foi favorável. A proporção de participantes com pelo menos um evento adverso foi semelhante entre vosoritida e placebo; a maioria dos eventos foi leve ou moderada, com predomínio de reações locais transitórias no sítio de injeção. Eventos adversos graves foram mais frequentes no placebo e nenhum foi atribuído ao medicamento do estudo; não houve eventos grau 4 nem óbitos. A imunogenicidade mostrou anticorpos anti-droga em aproximadamente 42% dos pacientes em uma ou mais visitas, sem detecção de anticorpos neutralizantes e sem associação com resposta de crescimento ou com hipersensibilidade/reacção local, o que mitiga preocupações quanto a impacto clínico. A descontinuação definitiva por evento adverso foi rara e relacionada a ansiedade às injeções em um único participante, sem padrão de risco emergente atribuível ao fármaco. Uma visão da incidência geral de eventos adversos é apresentada na [Tabela 31, no ANEXO II](#).

**Em conjunto, os autores concluíram que a vosoritida aumentou significativamente a VCA e o escore Z de altura em 52 semanas, sem efeitos negativos sobre a proporcionalidade ou maturação óssea e com boa**



tolerabilidade; os efeitos vasculares relatados foram leves, autolimitados e clinicamente pouco relevantes.

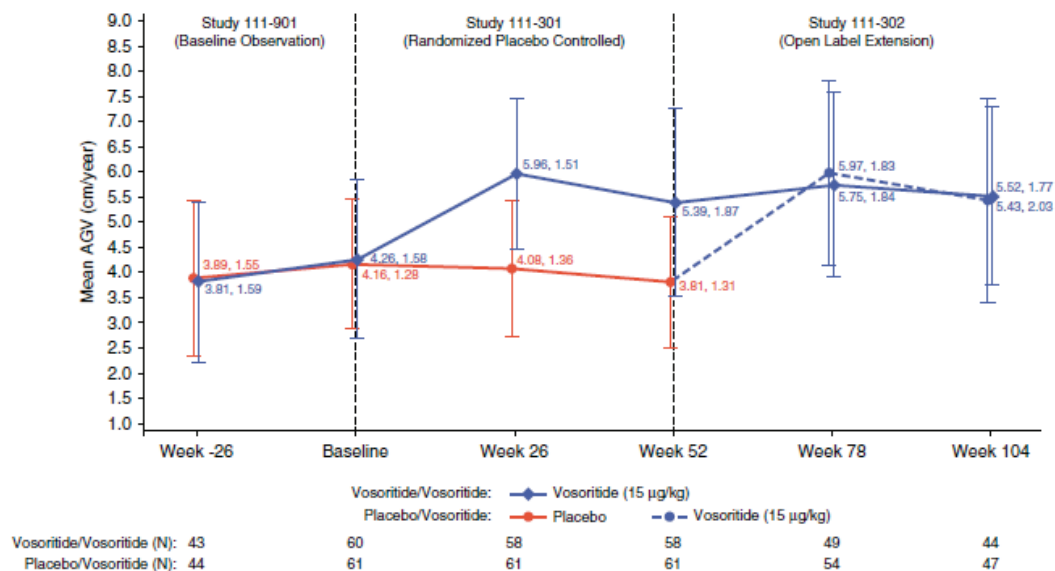
**111-302 – Extensão do estudo de fase III (3 publicações)**

**Savarirayan et al., 2021 – 2 anos de acompanhamento**

Após as 52 semanas do estudo duplo-cego, todos os participantes foram elegíveis para a extensão aberta 111-302, recebendo vosoritida 15 µg/kg/dia. O objetivo foi verificar a manutenção do efeito de crescimento e a segurança com tratamento contínuo por dois anos, além de observar o comportamento dos participantes que trocaram do placebo para a vosoritida.

A dinâmica de VCA observada no estudo controlado foi mantida na extensão: entre os previamente tratados, a VCA média permaneceu na faixa de ~5,5 a 5,8 cm/ano aos 18 e 24 meses; entre os que migraram do placebo para vosoritida, a VCA aumentou para patamar semelhante ao observado no braço ativo inicial, sugerindo captura do efeito após o início da terapia. Essa convergência é clinicamente relevante por demonstrar que o benefício não depende exclusivamente da exposição inicial e que a introdução subsequente do tratamento também resulta em aceleração do crescimento (*Figura 9*).

**Figura 9. Gráfico de linha da velocidade média de crescimento anual mostrada em intervalos de 6 meses começando no estudo de observação de linha de base e continuando através do estudo randomizado controlado por placebo por 52 semanas e, em seguida, no estudo de extensão por um total de 104 semanas, exibido pelo braço de tratamento derivado de dados observados.**



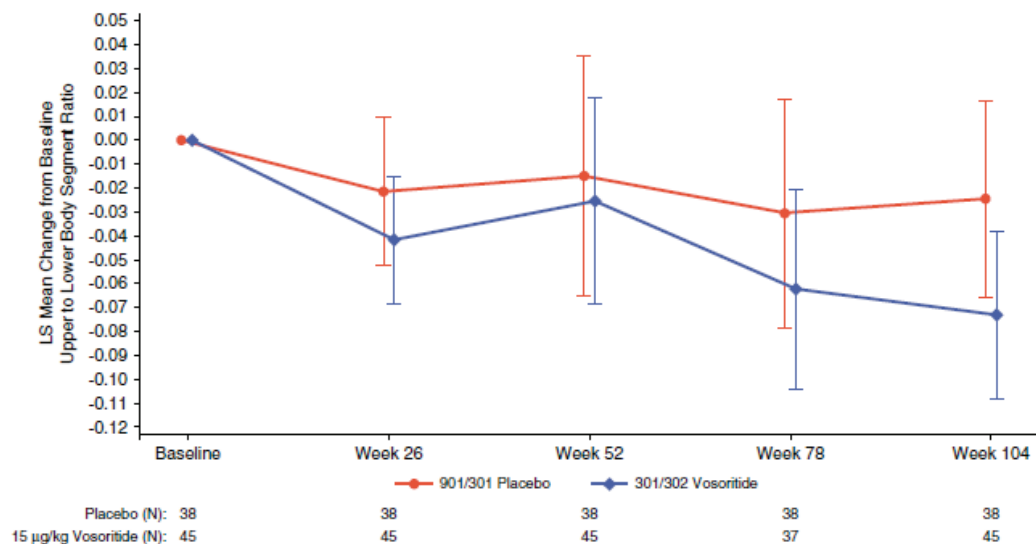


As análises comparativas em 24 meses, ancoradas no mesmo modelo ajustado utilizado no pivotal, mostraram ganho adicional de altura de ~3,5 cm no grupo tratado em relação a crianças não tratadas ao longo de período comparável, com diferença média ajustada de 3,34 cm e intervalo de confiança estreito, corroborando magnitude e precisão do efeito acumulado. Em paralelo, observou-se melhora adicional do escore Z de altura com diferença ajustada de +0,44 em 104 semanas, consistente com o incremento contínuo da velocidade.

A proporcionalidade corporal também evoluiu favoravelmente. A razão entre segmentos superior e inferior apresentou redução média adicional no grupo tratado, com diferença ajustada de -0,05 aos 24 meses versus controles históricos, compatível com diminuição da desproporção. Em termos funcionais, esse achado indica que o segmento inferior (membros) acelera sem deteriorar o tronco, aproximando o fenótipo de uma distribuição mais equilibrada de crescimento (*Figura 10*).



**Figura 10. Gráfico de linha mostrando a análise de covariância (ANCOVA) LS mudança média da linha de base com intervalos de confiança de 95% para a proporção do segmento corporal superior para inferior em intervalos de 6 meses para um total de 24 meses e exibida pelo braço de tratamento.**



A segurança ao longo de dois anos permaneceu consonante com o perfil observado no pivotal. Não emergiram novos sinais de risco; a maioria dos eventos adversos foi leve e o evento mais comum continuou a ser reação transitória no local da injeção. Não houve eventos adversos graves atribuídos ao tratamento. A idade óssea, avaliada por método de Greulich & Pyle, progrediu normalmente em meninos e meninas, sem indícios de aceleração patológica de maturação.

**Em síntese, os autores concluíram que a vosoritida manteve o benefício em VCA e escore Z de altura por ao menos dois anos, com melhora de proporcionalidade e boa tolerabilidade contínua.**

**Savarirayan *et al.*, 2024 – Benefício em Qualidade de Vida**

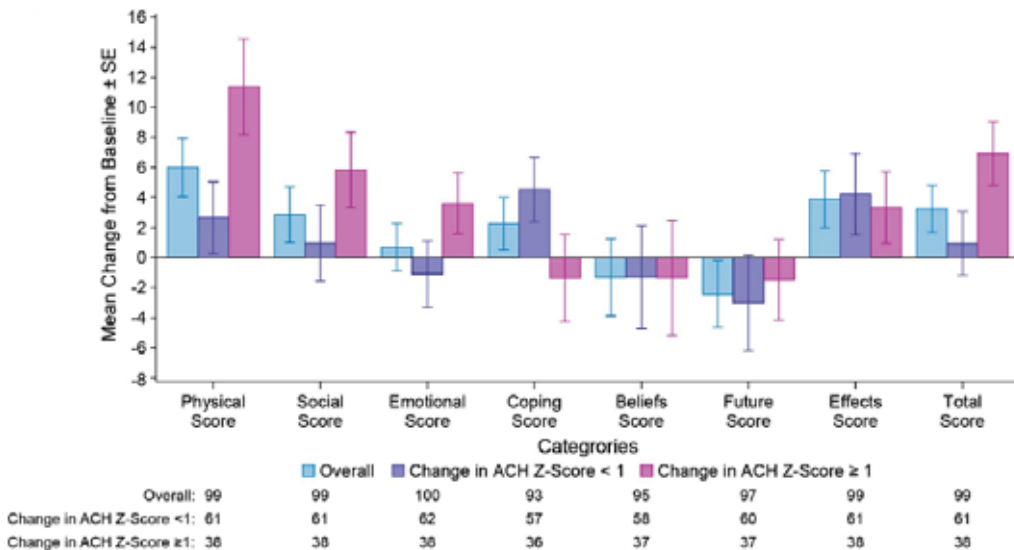
A avaliação publicada em 2024 examinou o impacto em qualidade de vida relacionada à saúde após aproximadamente três anos de tratamento contínuo com vosoritida no contexto do 111-302. Os dados foram coletados de 119 participantes, com idade média de 9,2 anos no início, utilizando o questionário QoLISSY nas versões para cuidadores e auto-relato, com foco em domínios físico, social e emocional e em uma pontuação total composta.

Os resultados demonstraram melhorias significativas em qualidade de vida ao terceiro ano, especialmente nos domínios físico e social, coerentes com o benefício de

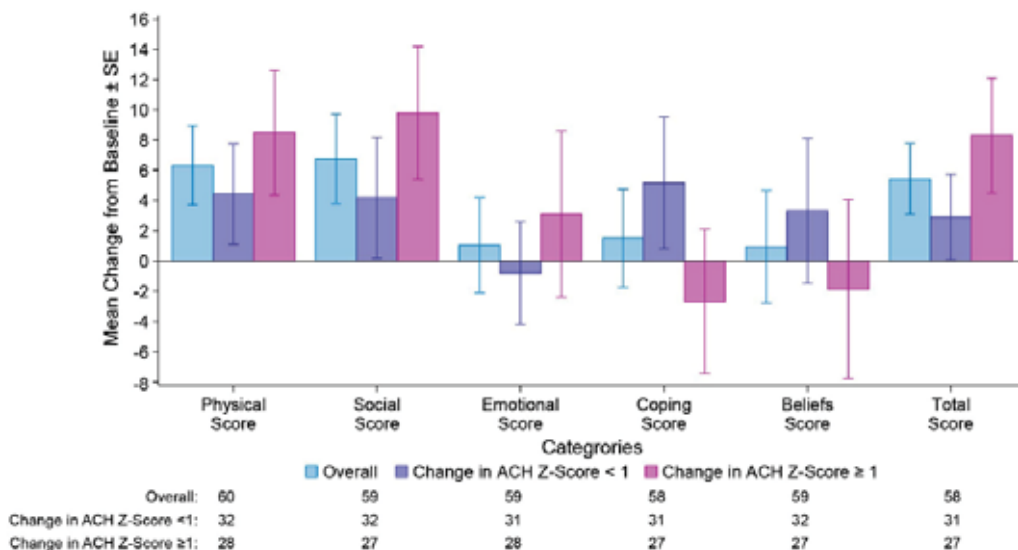


crescimento observado. A pontuação total aumentou tanto por relato de cuidadores quanto por auto-relato, e o efeito foi mais pronunciado no subgrupo com ganho  $\geq 1$  DP no escore Z de altura no momento da análise, reforçando a tese de que maior resposta de crescimento se traduz em benefício percebido na vida diária (*Figura 11* e *Figura 12*).

**Figura 11. Mudança média em relação ao início no QoLISSY no 3º ano, geral e por mudança no escore Z de altura da acondroplasia tratada com vosoritida, segundo relato dos cuidadores**



**Figura 12. Mudança média em relação ao início no QoLISSY no 3º ano, geral e por mudança no escore Z de altura da acondroplasia tratada com vosoritida, segundo auto-relato**





Especificamente, as mudanças médias nas pontuações físicas foram superiores a cinco pontos em ambas as fontes de relato na população global, com incrementos ainda maiores no subgrupo de maior ganho de estatura; as pontuações sociais também aumentaram de modo consistente, com amplitude maior nos auto-relatos. Uma análise complementar indicou que participantes com melhora de proporcionalidade mais acentuada exibiram incrementos médios maiores nas pontuações totais, sugerindo que o ganho proporcional pode contribuir para resultados funcionais e psicossociais além do ganho absoluto de altura.

A segurança permaneceu favorável no período analisado, sem eventos adversos graves relacionados ao tratamento.

**O conjunto de evidências, portanto, associa o benefício antropométrico sustentado a melhorias percebidas de qualidade de vida, especialmente quando há ganho de estatura mais expressivo e redução da desproporção corporal.**

#### **Savarirayan *et al.*, 2025 – 4 anos de acompanhamento [7]**

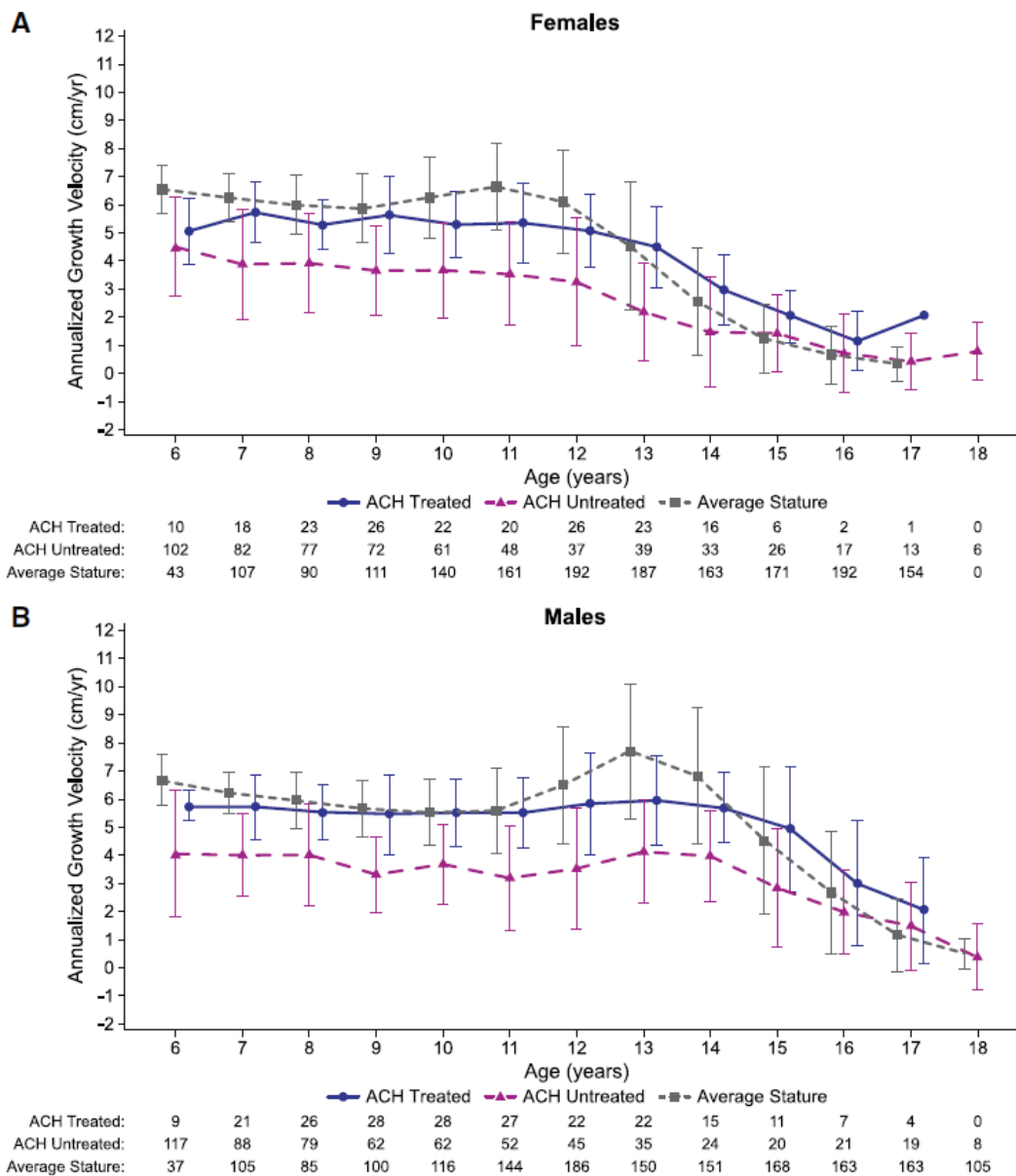
A publicação de 2025 atualizou os resultados do 111-302 com quatro anos de acompanhamento (e exposição máxima de até 6,2 anos em alguns participantes), consolidando evidências de sustentação do efeito e consistência de segurança no longo prazo. Participaram 119 crianças e adolescentes tratados com vosoritida 15 µg/kg/dia; a adesão foi alta e a taxa de permanência atingiu ~97% até o corte.

Os dados mostraram que a VCA sob tratamento se aproxima da de crianças sem acondroplasia antes da puberdade e se mantém consistentemente acima da de crianças com acondroplasia não tratadas, em ambos os sexos. A diferença média de VCA entre tratados e não tratados foi de ~1,84 cm/ano em meninos e ~1,44 cm/ano em meninas. Extrapolando essa diferença ao período de 11 anos, estimou-se um ganho adicional de altura de ~20 cm em meninos e ~16 cm em meninas, valores clinicamente relevantes.

A publicação também observou que, em determinados períodos, a VCA de crianças tratadas ultrapassou a VCA de referência de crianças sem acondroplasia, sobretudo após o estirão puberal, demonstrando benefício contínuo até o fechamento das epífises, o que potencialmente contribui para acelerar a convergência de estatura ao longo do acompanhamento ([Figura 13](#)). Em análises de associação, a VCA basal mais baixa correlacionou-se com maior incremento subsequente sob vosoritida, sugerindo que pacientes com maior déficit inicial podem se beneficiar de forma ainda mais pronunciada ([Figura 39, no ANEXO II](#)).



**Figura 13. Velocidade média de crescimento anualizada por idade e sexo durante o tratamento com vosoritida**



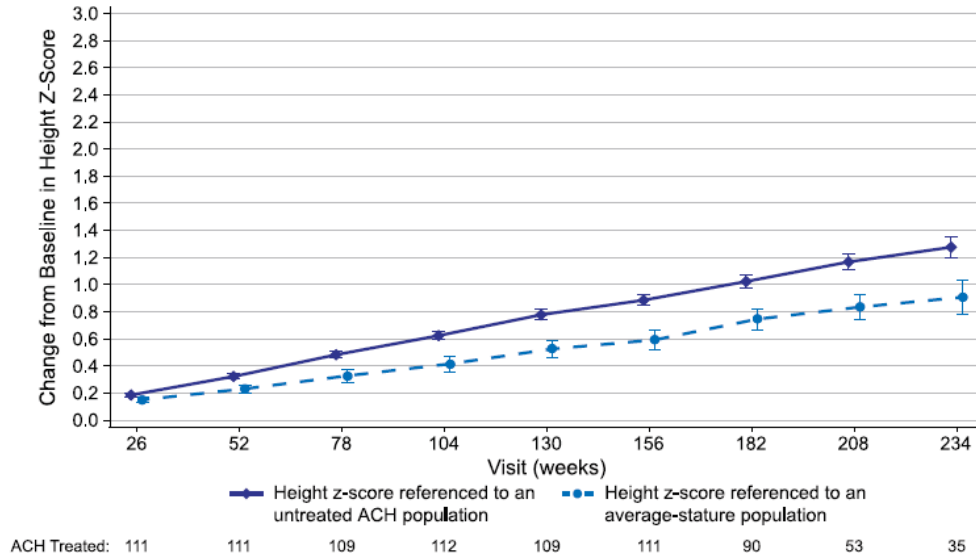
Velocidade média (DP) de crescimento anualizada por idade em participantes em tratamento com vosoritida (conjunto de análise completa 111-302), participantes não tratados com acondroplasia (CLARITY) e crianças de estatura média (Kelly et al.) em (A) mulheres e (B) homens. ACH, acondroplasia.

O escore Z de altura apresentou melhoras contínuas ao longo do tempo quando comparado tanto à referência de acondroplasia não tratada quanto ao padrão de estatura média. Em torno de 3 e 4,5 anos, os incrementos médios versus acondroplasia não tratada foram de ~0,89 e ~1,28, respectivamente, e versus estatura média de ~0,59



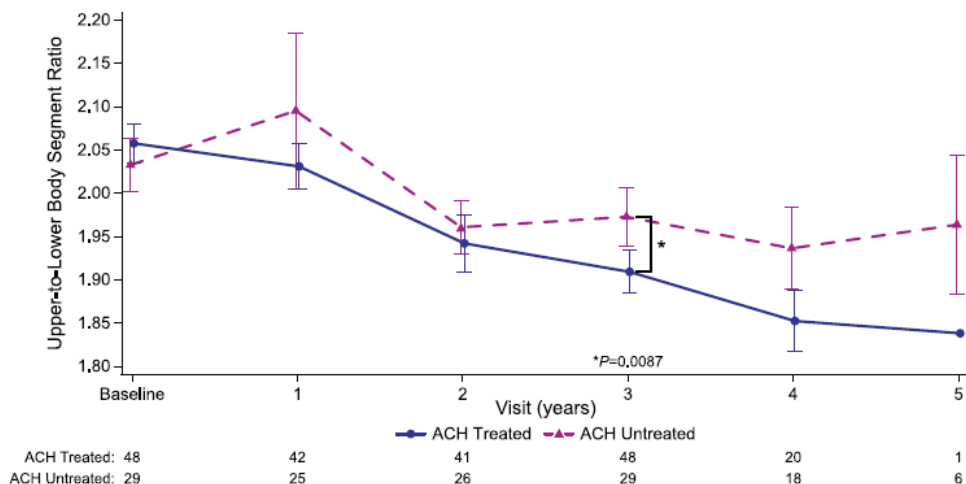
e  $\sim 0,91$ , indicando convergência gradual em ambas as perspectivas de referência (*Figura 14*).

**Figura 14. Alteração da linha de base no escore Z de altura na população tratada comparada a uma população com acondroplasia não tratada e a uma população de estatura média (conjunto de análise completa 111-302)**



A proporcionalidade corporal continuou a melhorar. As mudanças médias na razão S/I foram negativas nos diferentes estratos etários na linha de base, com magnitudes mais acentuadas nos mais jovens, e uma análise longitudinal padronizada aos 3 anos indicou diferença média ajustada de  $-0,09$  entre tratados e não tratados, além de uma mudança média de  $-0,15$  no grupo tratado versus  $-0,06$  no não tratado (*Figura 15*).

**Figura 15. Razão média (erro padrão) entre os segmentos superior e inferior do corpo em um subconjunto de crianças com avaliações em idade  $<11$  (meninas) ou  $<12$  anos (meninos) (tratados mais jovens) (estudo 111-302) e crianças não tratadas (estudo 111-901)**



O perfil de segurança de longo prazo manteve-se favorável. O evento adverso mais comum foi nasofaringite (~0,3 eventos por pessoa-ano). Eventos adversos graves ocorreram em ~18,5% dos participantes, geralmente atribuídos à condição de base e sem óbitos. Marcadores ósseos laboratoriais permaneceram estáveis sem tendências indesejadas, a idade óssea progrediu de forma compatível com a idade cronológica e a densidade mineral óssea não mostrou alterações significativas ao longo do acompanhamento.

### 3.2.1.3 Estudo fase II com crianças > 5 anos (111-202)

#### Savarirayan *et al.*, 2019 [40]

O estudo 111-202 foi um ensaio multinacional de escalonamento de dose com 35 crianças entre 5 e 14 anos com acondroplasia, distribuídas em quatro coortes para receber vosoritida em doses diárias subcutâneas de 2,5, 7,5, 15,0 ou 30,0 µg/kg. Após 6 meses, ajustes de dose foram realizados conforme dados emergentes. O acompanhamento médio foi de 42 meses, com administração domiciliar pelos cuidadores. A segurança foi avaliada por eventos adversos, exames laboratoriais, sinais vitais, ECGs, ecocardiogramas e resposta imunológica.

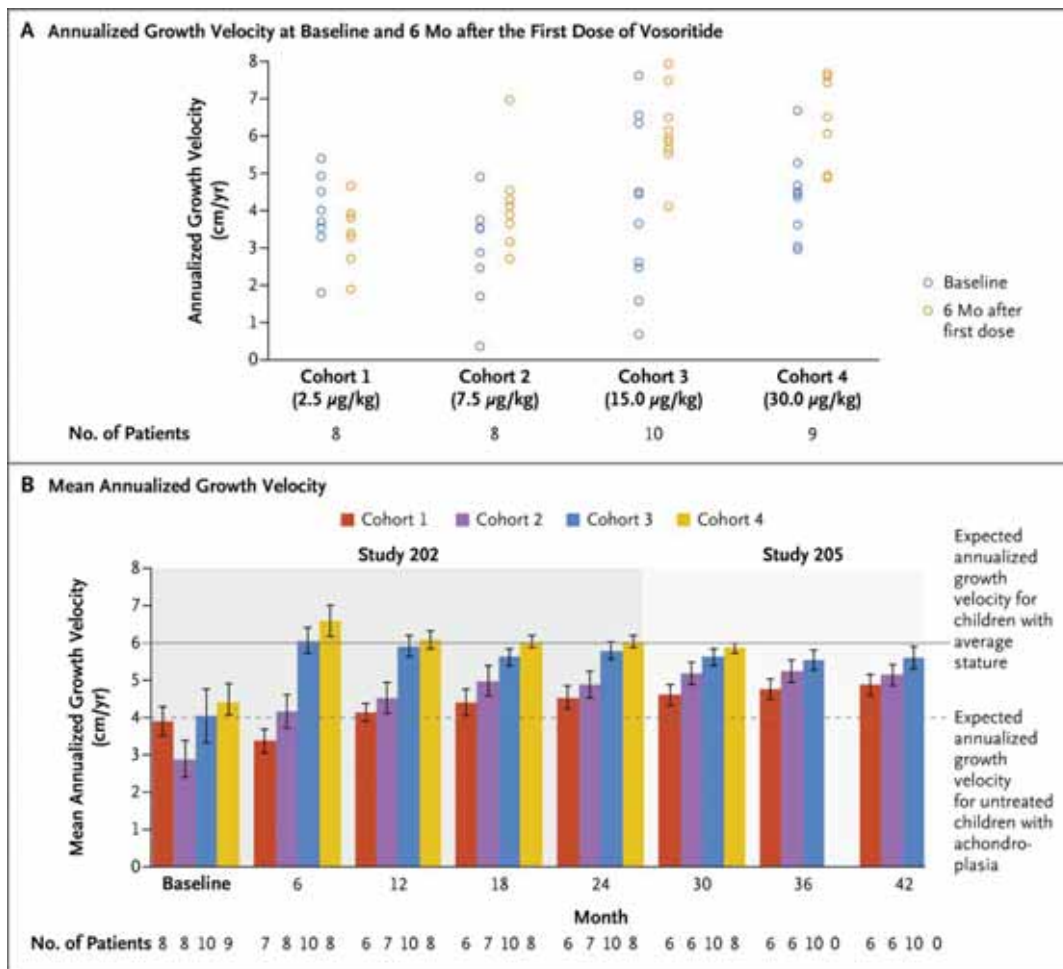
Todas as reações no local da injeção foram leves e transitórias. Anticorpos antidrogas foram detectados em 40% dos pacientes, sendo transitórios em metade dos casos. Anticorpos neutralizantes foram detectados em apenas dois pacientes, sem associação com eventos adversos ou resposta clínica. Alterações na pressão arterial foram transitórias e não resultaram em descontinuação. Eventos adversos graves ocorreram



em 11% dos pacientes, sem relação com crescimento desproporcional ou efeitos cardiovasculares significativos. (Apêndice: Tabela de segurança e imunogenicidade)

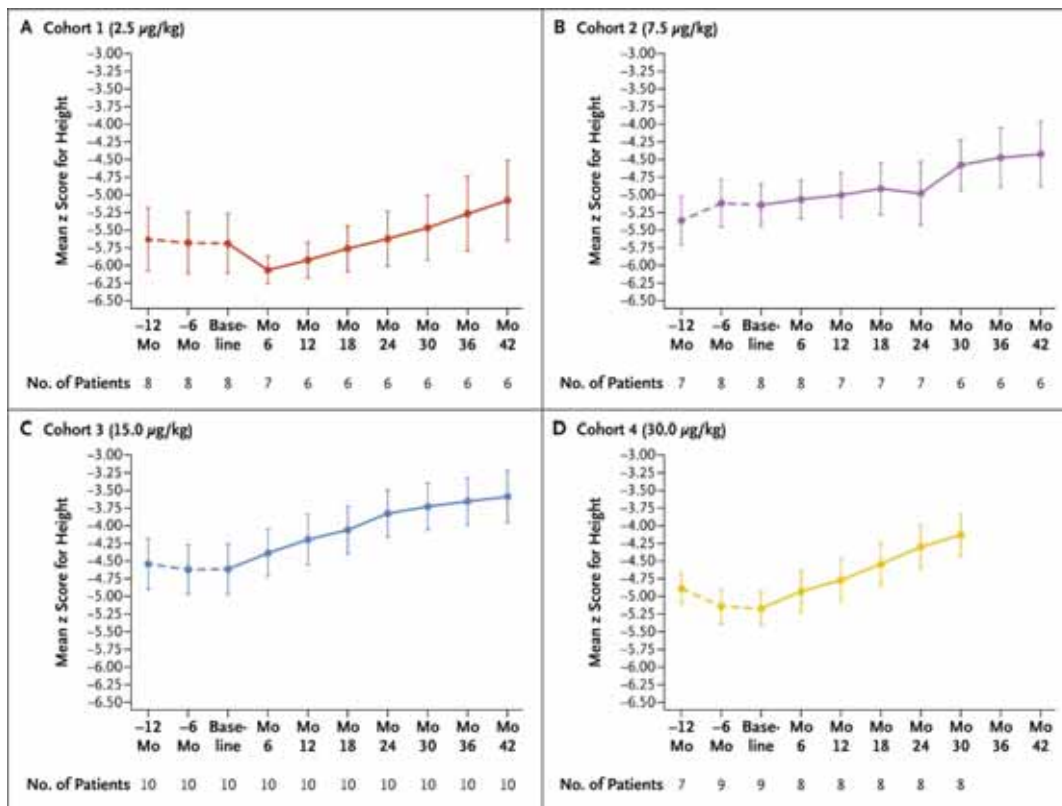
Durante os primeiros 6 meses, observou-se aumento dependente da dose na velocidade de crescimento anualizada (VCA), com ganhos de até 2,08 cm/ano nas coortes de maior dose. A VCA aumentou de forma sustentada por até 42 meses, com velocidade média de 5,51 cm/ano na coorte de 15 µg/kg entre os meses 30 e 42, representando um ganho de 1,46 cm/ano desde a linha de base (Figura 16).

Figura 16. Velocidade de crescimento anualizada (VCA) na linha de base e durante o período de tratamento.



O escore Z de altura também apresentou aumento dependente da dose nos primeiros 6 meses, com melhora sustentada por até 42 meses. O aumento médio foi de 1,03 na coorte de 15  $\mu\text{g}/\text{kg}$  e de 1,06 na coorte de 30  $\mu\text{g}/\text{kg}$ . As inclinações das linhas de regressão foram positivas em todas as coortes, indicando melhoria contínua ([Figura 17](#)).

Figura 17. Média do escore Z da altura na linha de base e durante o período de tratamento



A figura mostra as pontuações z médias para a altura durante os últimos 12 meses do estudo de crescimento observacional e durante o período de tratamento nas coortes 1, 2 e 3 a 42 meses (Painéis A a C) e na coorte 4 a 30 meses (Painel D).

O crescimento proporcional entre os segmentos superior e inferior do corpo foi mantido ao longo do estudo, sem alterações clinicamente relevantes na razão corporal.

Os autores concluíram que a vosoritida administrada diariamente por via subcutânea apresentou perfil de segurança favorável e resultou em aumento sustentado da VCA por até 42 meses.

### 3.2.1.4 Estudo fase II com crianças < 5 anos (111-206)

Savarirayan *et al.*, 2022 [132]

O estudo 111-206 foi um ensaio clínico fase II, randomizado, duplo-cego e controlado por placebo, conduzido em 16 centros internacionais com 75 crianças com acondroplasia menores de 60 meses. Os participantes foram divididos em três coortes por faixa etária e randomizados para receber vosoritida ou placebo por 52 semanas. A



dose foi de 30 µg/kg para crianças de até 23 meses e 15 µg/kg para crianças de 24 a 59 meses.

Eventos adversos ocorreram em todos os participantes, sendo predominantemente leves e transitórios, como reações locais. Eventos graves foram mais frequentes no grupo placebo (19%) do que no grupo vosoritida (7%). Um óbito ocorreu no grupo vosoritida, atribuído à condição clínica subjacente e não relacionado ao medicamento (*Tabela 33, no ANEXO II*).

A análise de ANCOVA mostrou uma diferença média de 0,25 no escore Z de altura entre vosoritida e placebo após 52 semanas, com consistência entre as coortes.

A VCA foi 0,78 cm/ano maior no grupo vosoritida em comparação ao placebo, indicando aceleração do crescimento linear.

A razão corporal superior-inferior apresentou diferença média de -0,07 entre os grupos, sugerindo melhora na proporcionalidade sem piora da desproporção.

Na coorte de crianças com menos de 6 meses, exames de imagem mostraram aumento de 44% no volume facial, 129% nos seios paranasais e 44% na área do forame magno no grupo vosoritida, em comparação a 34%, 48% e 25% respectivamente no grupo placebo. Esses achados sugerem benefício anatômico relevante.

**Os autores concluíram que crianças com acondroplasia de 3 a 59 meses tratadas com vosoritida por 52 semanas apresentaram perfil de segurança favorável e melhora no escore Z de altura e VCA, além de sugerir benefício anatômico relevante em volume facial, de seios paranasais e de área do forame magno.**

### **3.2.1.5 Estudo prospectivo independente**

#### **Sawamura et. al., 2025 – estudo prospectivo no Japão [129]**

Sawamura e colaboradores realizaram um estudo prospectivo com crianças japonesas com acondroplasia tratadas com vosoritida, com foco adicional em alinhamento espinhal e membros inferiores. Após 18 meses de tratamento, observou-se melhora na VCA e escore Z de altura, com incremento médio de +0,52 no escore Z e VCA média de 6,0 cm/ano (*Tabela 8*).

**Tabela 8. Comparação de parâmetros entre antes do início e um ano após início de tratamento. \*(°) = graus; \*\*mm = milímetros**

Parâmetro	Antes (média ± DP)	Após 12 meses (média ± DP)	Mudança (média ± DP)	Valor p
Altura (escore Z para acondroplasia)	0,2 ± 1,4	0,5 ± 1,3	+0,3 ± 0,2	<0,01
Cervical lordose (°)	11,5 ± 15,8	12,9 ± 9,5	+1,5 ± 17,3	0,74
Cifose torácica (°)	30,4 ± 15,2	29,1 ± 10,3	-1,3 ± 13,8	0,71
Cifose toracolombar (°)	27,6 ± 15,8	24,8 ± 15,9	-2,8 ± 7,5	0,15
Lordose lombar (°)	53,5 ± 18,5	48,3 ± 19,2	-5,2 ± 7,0	0,01
Inclinação pélvica (°)	6,0 ± 17,8	3,8 ± 18,7	-2,2 ± 8,4	0,30
Incidência pélvica (°)	56,6 ± 19,9	53,9 ± 19,1	-2,6 ± 9,6	0,31
Ângulo sacral (°)	50,6 ± 10,9	50,2 ± 9,9	-0,4 ± 4,2	0,69
Eixo sagital C7 (mm)	6,6 ± 23,9	9,2 ± 17,0	+2,6 ± 17,9	0,26
Ângulo do eixo mecânico (MAA, °)	7,3 ± 9,0	3,9 ± 6,8	-3,4 ± 4,3	<0,01
Ângulo femoral proximal lateral (°)	83,9 ± 16,8	85,6 ± 16,1	+1,7 ± 2,8	<0,01
Ângulo femoral distal lateral (°)	91,6 ± 5,9	88,8 ± 4,1	-2,8 ± 3,6	<0,01

Além do crescimento, os autores documentaram melhora no alinhamento da coluna vertebral e redução da angulação dos membros inferiores, com base em medidas radiográficas seriadas ([Tabela 8](#)). A segurança foi favorável, com eventos adversos leves e sem novos sinais de risco. A adesão ao tratamento foi alta, com mais de 96% das doses administradas conforme prescrição.

### 3.2.1.6 Evidência de Mundo Real (RWE)

#### **Cormier-Daire et. al., 2025 – estudo de mundo real na França [128]**

Valérie Cormier-Daire e colaboradores descreveram os resultados do programa de acesso expandido (EAP) de vosoritida na França. Nesse estudo, foram incluídas crianças com acondroplasia geneticamente confirmada, com 5 anos ou mais e epífises abertas, tratadas com vosoritida subcutânea diária na dose de 15 µg/kg. O acompanhamento clínico foi realizado por 12 meses, com coleta de dados de segurança e eficácia em visitas nos meses 1, 3, 6 e posteriormente a cada 6 meses.

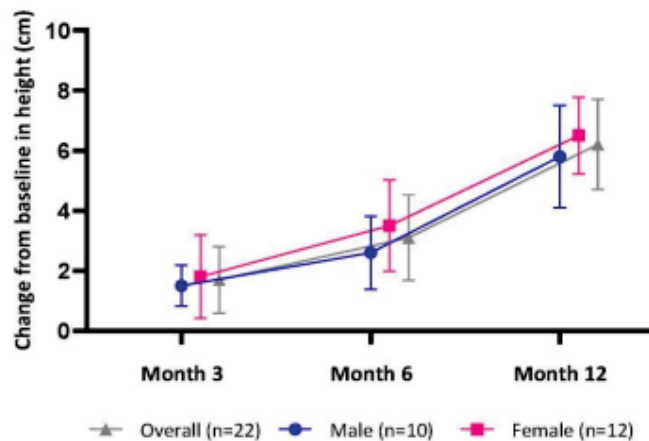
O tratamento foi iniciado em ambiente hospitalar e posteriormente autoadministrado em casa pelos pais ou cuidadores, após treinamento. Dos 62 participantes inscritos, 57



iniciaram o tratamento durante o EAP e 5 após a comercialização. A média de idade no início foi de 8,6 anos, com distribuição equilibrada entre os sexos. A duração média de tratamento foi de 277 dias, e 14 participantes deixaram de tomar um total de 43 doses ao longo do período. Todos os eventos adversos foram leves, principalmente reações no local da injeção, e não houve descontinuações relacionadas ao tratamento (*Tabela 32, no ANEXO II*).

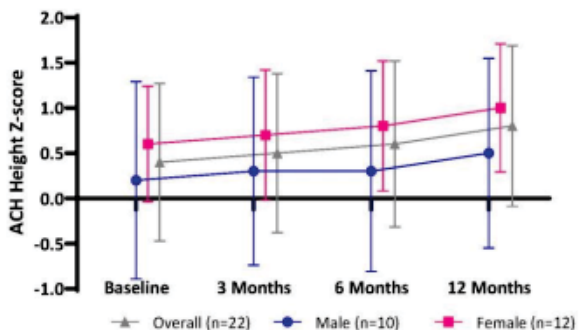
Entre os participantes que completaram pelo menos 6 meses de tratamento, observou-se um aumento médio de altura de 3,2 cm, com velocidade de crescimento anualizada (VCA) de 6,2 cm/ano. Para aqueles que completaram 12 meses, o aumento médio foi de 6,2 cm, com VCA de 6,0 cm/ano. Dados adicionais coletados post hoc aos 18 meses mostraram um aumento médio de 8,8 cm (*Figura 18*).

**Figura 18. Mudança em altura**



Nos 22 participantes que completaram pelo menos 12 meses de tratamento, o escore Z de altura aumentou em média 0,39, com ganho de 0,30 para meninos e 0,46 para meninas (*Figura 25*).

**Figura 19. Escore Z de altura**

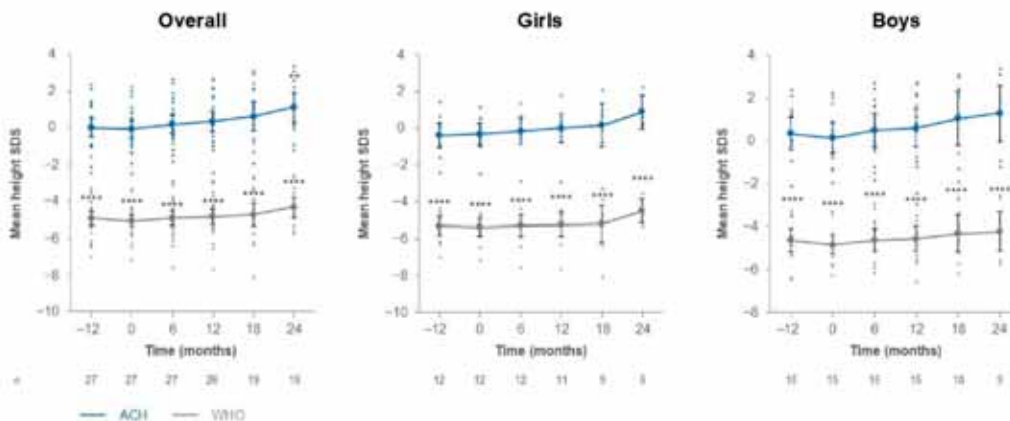


Os autores concluíram que, neste primeiro acompanhamento em cenário de mundo real, a vosoritida apresentou um perfil de risco-benefício positivo semelhante ao observado nos ensaios clínicos, com aumento sustentado de crescimento e boa tolerabilidade.

**Rua *et. al.*, 2025 – estudo de mundo real em Portugal [131]**

O estudo descreve dados de mundo real sobre o uso de vosoritida em Portugal, com foco em crescimento, segurança e adesão. Foram incluídas crianças com acondroplasia tratadas por até 24 meses. A velocidade de crescimento anualizada (VCA) aumentou significativamente após o início do tratamento, com média de 6,1 cm/ano no primeiro ano e 5,8 cm/ano no segundo ano. O escore Z de altura também melhorou, com incremento médio de +0,42 após 12 meses e +0,71 após 24 meses ([Figura 20](#)).

**Figura 20. Altura média absoluta DP em crianças (n = 27) tratadas com vosoritida por até 24 meses**



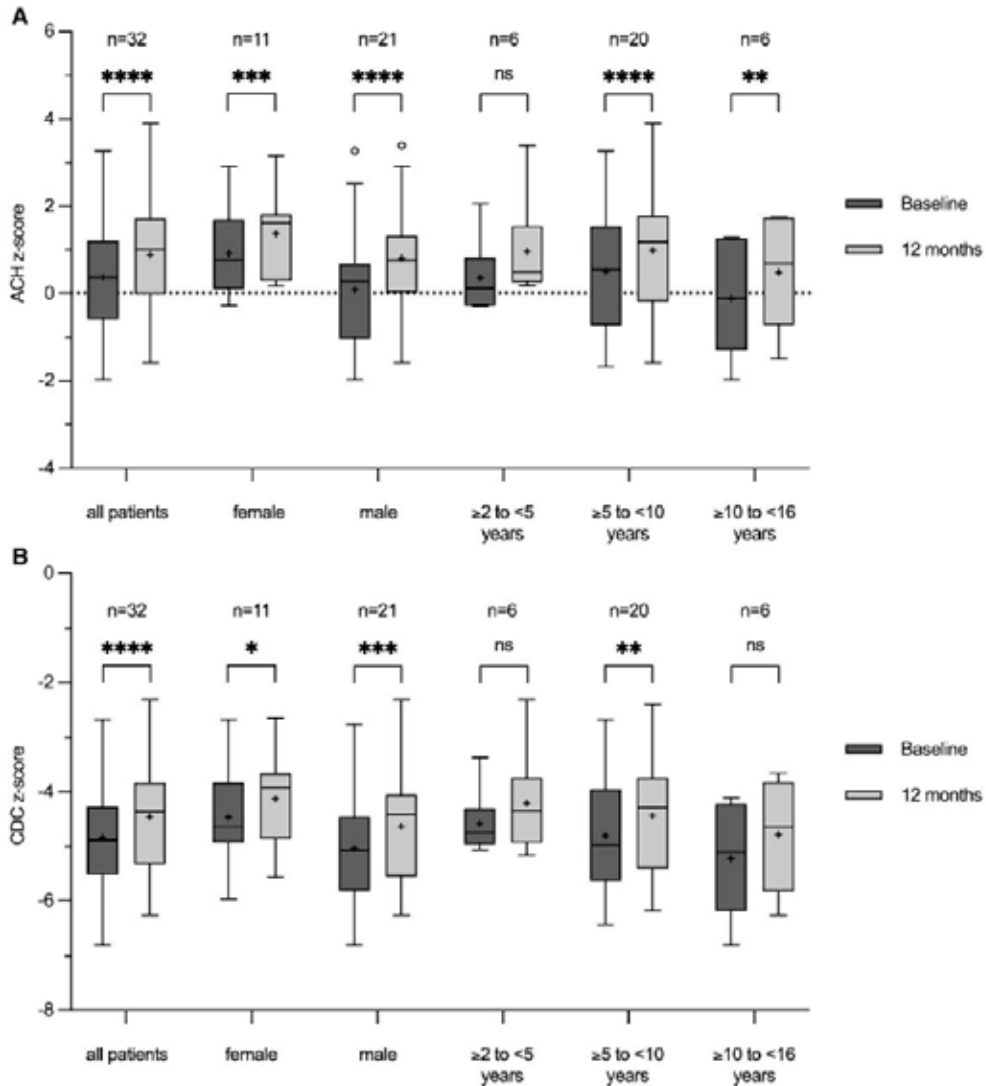
A adesão ao tratamento foi alta, com mais de 95% das doses administradas conforme prescrição. Os eventos adversos foram leves e autolimitados, principalmente reações locais no local da injeção. Não houve eventos adversos graves relacionados ao tratamento.

**Os autores concluíram que a vosoritida foi bem tolerada e eficaz em promover crescimento em crianças com acondroplasia em ambiente clínico real.**

**Reincke *et. al.*, 2025 – estudo de mundo real na Alemanha [130]**

Reincke e colaboradores conduziram um estudo retrospectivo com crianças tratadas com vosoritida por 12 meses na Alemanha. A VCA média aumentou de 3,9 cm/ano na linha de base para 5,7 cm/ano após 12 meses de tratamento, com diferença média de +1,8 cm/ano (*Figura 21*).

**Figura 21. Gráficos de caixa dos escores z da altura na linha de base (cinza mais escuro, à esquerda) e no mês 12 (cinza mais claro, à direita)**



O escore Z de altura também apresentou melhora significativa, com incremento médio de +0,45. A segurança foi consistente com os dados de ensaios clínicos, com eventos adversos leves e sem descontinuações relacionadas ao tratamento. A adesão foi superior a 90% ao longo do período avaliado.

**Além dos parâmetros de crescimento, os autores avaliaram função física e qualidade de vida por meio de questionários específicos, observando melhora nos domínios de mobilidade e bem-estar social.**

### 3.2.1.7 Qualidade da evidência

A classificação da qualidade da evidência foi feita por desfecho conforme apresentado na Tabela 9. A tabela completa conforme a metodologia GRADE encontra-se no [ANEXO VI](#).

#### Contexto e considerações

Por se tratar de uma doença crônica e de um tratamento de longo prazo com benefícios esperados para toda a vida, optou-se por incluir os estudos de fase II e suas extensões de longo prazo, bem como a extensão aberta de longo prazo do estudo de fase III, neste dossiê, a fim de se ter o maior e melhor conjunto de dados disponível. Adicionalmente, sabe-se que existem limitações na aplicação do GRADE no contexto das doenças raras, fato que tem sido observado por membros da Comissão de Medicamentos da CONITEC e pareceristas nas recentes avaliações de medicamentos indicados para estas doenças.

Vosoritida tem um estudo pivotal de fase III randomizado controlado por placebo e duplo cego em seu programa clínico, o que pode ser considerado uma fortaleza, devido às conhecidas dificuldades de se realizar estudos de alta qualidade metodológica e amostras grandes em doenças raras. Em reconhecimento a este fato, foi considerado apenas o estudo de fase III para a avaliação dos desfechos relacionados à altura (escore Z de altura e VCA), o que gerou uma qualidade de evidência alta. Para os demais desfechos foram considerados também os estudos de fase II, que incluem um estudo sem grupo controle, o que gerou uma qualidade de evidência baixa.

**Tabela 9. Classificação da qualidade das evidências.**

Desfecho	Classificação
Escore Z de altura	(X) Alta ( ) Moderada ( ) Baixa ( ) Muito baixa
Velocidade de crescimento anualizada	(X) Alta ( ) Moderada ( ) Baixa ( ) Muito baixa
Relação segmento superior:segmento inferior do corpo	( ) Alta ( ) Moderada (X) Baixa ( ) Muito baixa
Qualidade de vida	( ) Alta ( ) Moderada (X) Baixa ( ) Muito baixa
Segurança e tolerabilidade	( ) Alta ( ) Moderada (X) Baixa ( ) Muito baixa

Fonte: elaboração própria.

### 3.3 Evidências adicionais

Neste subitem são apresentadas as comunicações científicas mais recentes, em complemento aos manuscritos e periódicos, corroborando para a demonstração da eficácia sustentada em mais longo prazo. Também são incluídos dados recentes de vida real que ainda não foram disponibilizados em periódicos e, portanto, não constaram na revisão sistemática.

#### 3.3.1 111-205 – Extensão do estudo fase II com crianças > 5 anos (111-202)

##### Hoover-Fong *et al.*, 2024 – 7 anos de acompanhamento (pôster) [135]

Na análise mais recente de longo prazo, o tratamento com vosoritida continuou bem tolerado, sem evidências de maturação esquelética acelerada ou eventos adversos graves atribuíveis ao fármaco após sete anos de acompanhamento (Figura 41, no ANEXO II). A velocidade de crescimento anualizada (VCA) média específica por idade e sexo em crianças tratadas foi maior do que a VCA média correspondente em crianças não tratadas da mesma idade e sexo em todos os grupos etários entre 6 e 14 anos (Figura 22). A diferença média entre grupos etários inteiros foi de 1,63 cm/ano para meninos e 1,33 cm/ano para meninas. A mudança desde os escores Z de altura iniciais foi de +1,02 no mês 84 em relação à população de estatura média e +1,67 em relação à população com acondroplasia não tratada (Figura 23). Observou-se também uma tendência de melhora na proporcionalidade corporal ao longo do tempo, com redução média de -0,21 na razão segmento superior/inferior no mês 84 (Figura 42, no ANEXO II). Uma análise comparativa ajustada às diferenças de linha de base demonstrou um ganho adicional de estatura de 11,03 cm (IC 95%: 8,62–13,45) em 17 indivíduos.



Figura 22. A média do intervalo de 12 meses da VCA em crianças tratadas com vosoritida é maior em comparação com crianças não tratadas da mesma idade.

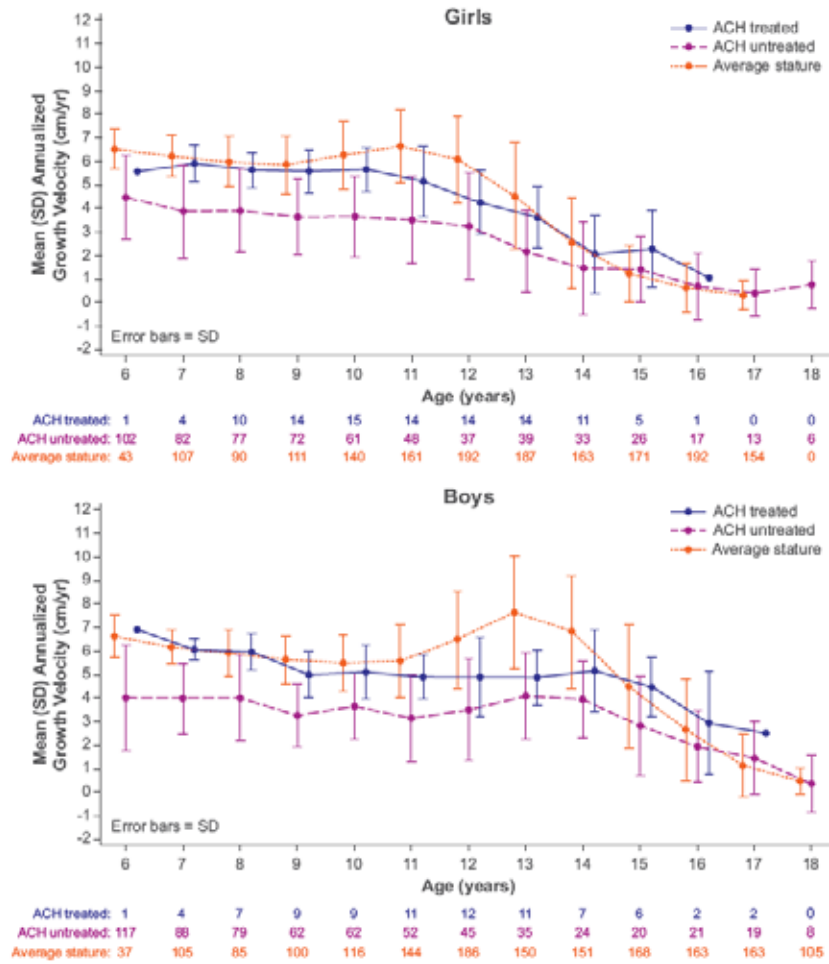
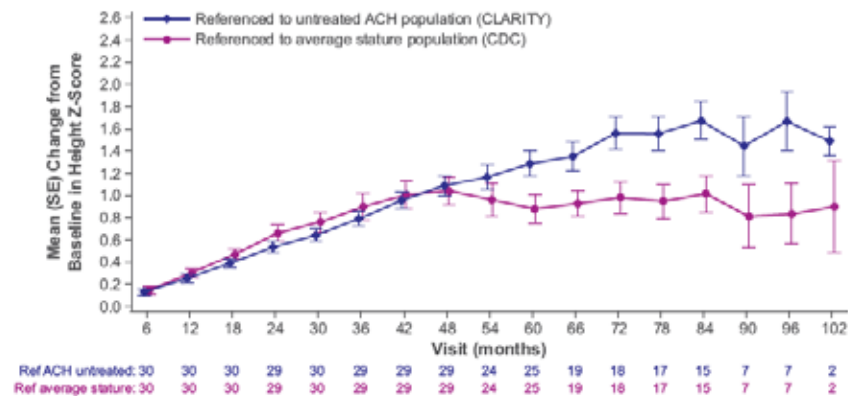


Figura 23. O escore Z de altura aumentou ao longo do tempo





### **3.3.2 111-208 – Extensão do estudo fase II com crianças < 5 anos (111-206) [123]**

#### **Savarirayan et al., 2024 – 4 anos de acompanhamento (pôster) [123]**

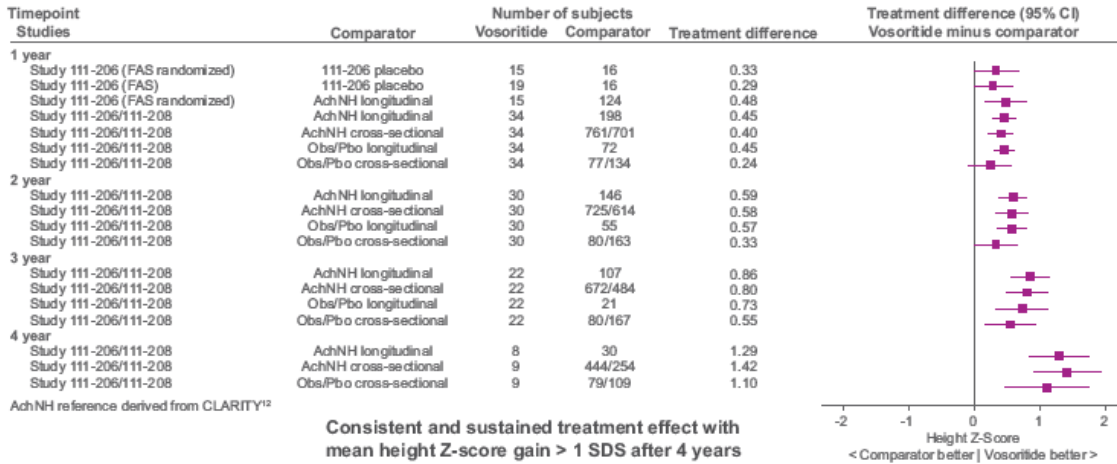
Na fase de extensão do estudo com crianças menores de cinco anos, as injeções diárias de vosoritida foram bem toleradas, sem eventos adversos que limitassem o tratamento. Não foram observados novos problemas de segurança, e os efeitos adversos mais frequentes foram reações leves e autolimitadas no local da injeção.

O tratamento demonstrou efeito consistente e duradouro sobre o crescimento, especialmente em crianças que iniciaram antes dos cinco anos, reforçando o benefício do início precoce. As proporções corporais permaneceram estáveis ao longo do tempo. O escore Z de altura aumentou de forma consistente em comparação aos controles (Figura 30), e a altura absoluta também apresentou incremento ao longo do tempo (Figura 31).



Figura 24. O escore Z de altura aumentou consistentemente ao longo do tempo em crianças tratadas em comparação com os controles.

**Children ≥ 2 years at start of treatment**



**Children < 2 years at start of treatment**

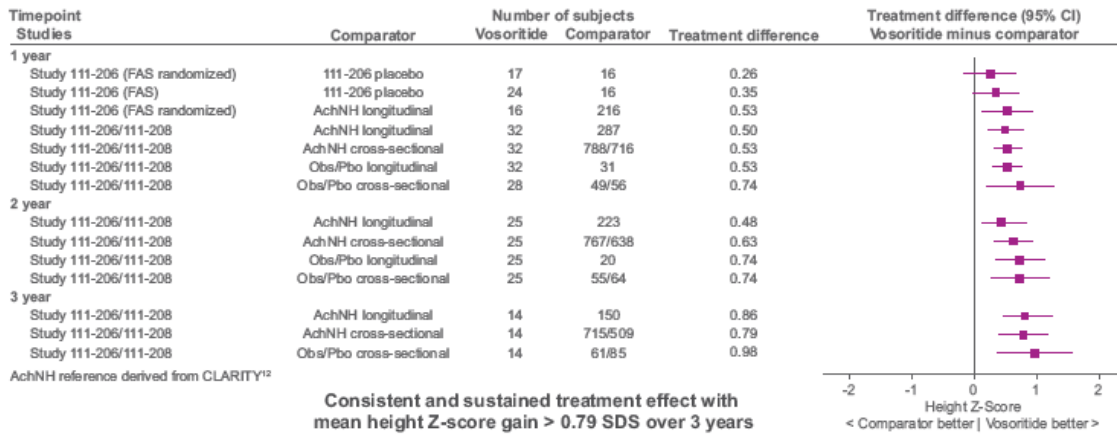
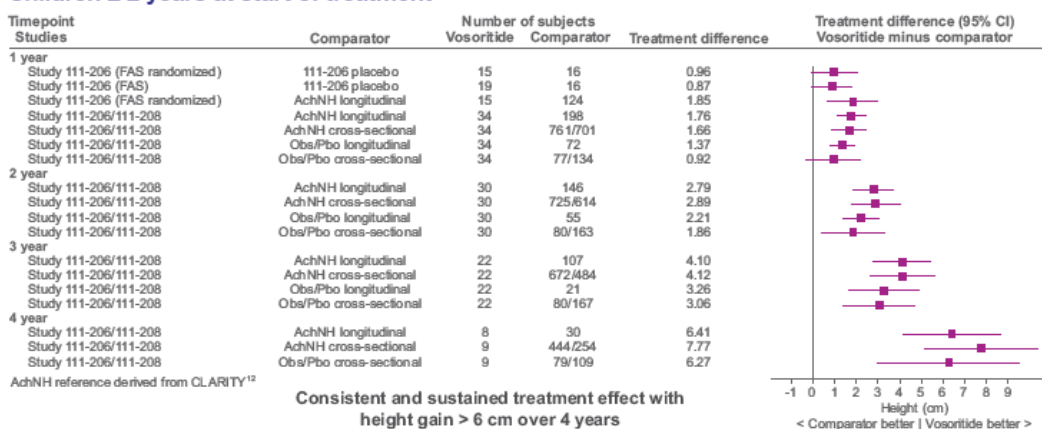


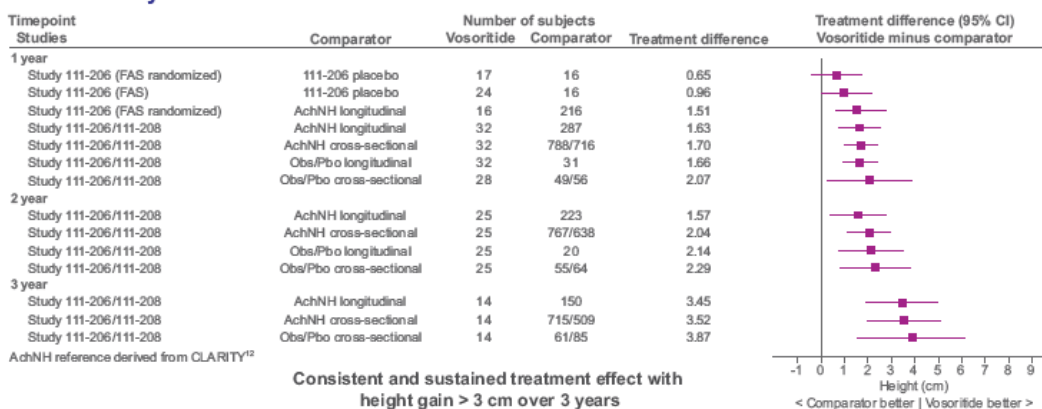


Figura 25. A altura aumentou ao longo do tempo em crianças tratadas em comparação com os controles

**Children ≥ 2 years at start of treatment**



**Children < 2 years at start of treatment**



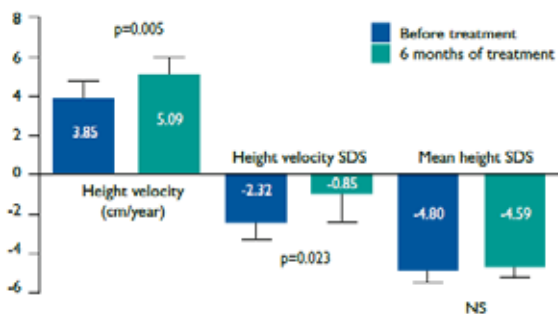
**3.3.3 Evidência de Mundo Real (RWE) – complementares ao identificado na Revisão Sistemática da Literatura (RSL)**

**Bordallo *et al.*, 2024 – estudo brasileiro [45]**

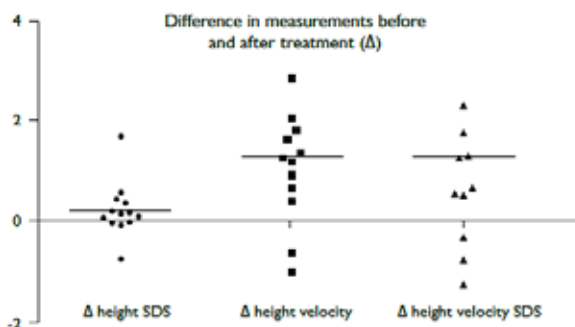
O pôster de Bordallo e colaboradores avaliou a resposta de crianças brasileiras com acondroplasia ao tratamento com vosoritida em cenário real. Vinte e três crianças entre 2 e 10 anos foram tratadas conforme a bula da ANVISA. Após seis meses de tratamento, observou-se aumento significativo na velocidade de crescimento, que passou de 3,85 para 5,09 cm/ano (*Figura 26*), e melhora no escore Z da velocidade de crescimento, de -2,32 para -0,85. Não houve diferença significativa na altura padronizada após seis meses. A análise individual mostrou variações positivas em altura, velocidade de crescimento e escore Z (*Figura 27*). Oito pacientes apresentaram hipertricrose, três relataram dor local, e não houve descontinuações.



**Figura 26. Média ± desvio padrão da velocidade de crescimento (cm/ano), DP da velocidade de crescimento e DP da altura antes e após 6 meses de tratamento com vosoritida (n=12)**



**Figura 27. Δ altura DP (-0,74 a +1,62), Δ velocidade de crescimento (-0,98 a +4,09), e Δ velocidade de crescimento DP (-1,23 a +5,63). n=12**



Os autores concluíram que o tratamento com vosoritida foi bem tolerado e aumentou significativamente a velocidade de crescimento e a velocidade de crescimento DP em pacientes com acondroplasia após 6 meses de tratamento.

**Mohnike *et al.*, 2024 – registro CrescNet [46]**

O registro europeu CrescNet incluiu 319 indivíduos com acondroplasia, dos quais 112 iniciaram tratamento com vosoritida após aprovação da EMA. Entre os tratados por 12 meses, o aumento médio de altura foi de 6,4 cm, com melhora de 0,2 no escore Z. Entre os tratados por 24 meses, o aumento foi de 11,0 cm, com melhora de 0,6 no escore Z.

Os dados indicam que os resultados em cenário real são consistentes com os achados dos ensaios clínicos.

**Allegri *et al.*, 2024 – estudo italiano [133]**

O estudo italiano de Allegri e colaboradores incluiu 30 pacientes com mais de seis meses de acompanhamento. A mediana de idade era de 8,9 anos, e os eventos



adversos foram limitados a reações locais transitórias. Não foram identificadas anormalidades cardíacas, e os dados de qualidade de vida ainda estão sendo coletados.

**Observou-se aumento significativo na altura, estabilidade na razão entre segmentos corporais e aumento no escore Z de peso.**

## 4. MODELO DE CUSTO-UTILIDADE

A avaliação de custo-efetividade da vosoritida em acondroplasia ( $\geq 6$  meses, epífises abertas) utiliza um modelo de simulação individual que captura o impacto da baixa estatura na QVRS e na incidência de complicações ao longo da vida [1, 12, 34]. A idade de fechamento de epífises foi definida em 17 anos (meninos) e 15 anos (meninas), com base na queda da velocidade de crescimento anual (VCA)  $< 1,5$  cm/ano, alinhada ao critério de interrupção em bula.

### 4.1 Métodos

#### 4.1.1 População, distribuição etária e subgrupos

População: pacientes com acondroplasia de 0,5 a 17 anos ao início do tratamento. A idade de início de tratamento foi definida como 6 meses (0,5 ano), em conformidade com a indicação aprovada em bula. Percentual de sexo masculino: 50,6% (estimativa Brasil 2025).

#### 4.1.2 Contexto/local e perspectiva

Não há tecnologia incorporada nem PCDT específico para acondroplasia no SUS. A perspectiva é a do SUS.

#### 4.1.3 Horizonte temporal e taxa de desconto

Horizonte vitalício (ciclos anuais), conforme manual do MS (doenças crônicas e desfechos de longo prazo) [133]. Desconto de 5% para custos e de 3% para desfechos; análises de sensibilidade nos seguintes cenários:

- 3% para custos e 0% para desfechos
- 1,5% para custos e desfechos
- 0% para custos e desfechos (diretriz brasileira)
- 5% para custos e desfechos (diretriz brasileira)
- 10% para custos e desfechos (diretriz brasileira)

### **Justificativa para o uso de 5%/3%**

O uso de 5% para custos é consistente com as diretrizes brasileiras e com a prática em várias jurisdições europeias de ATS, onde uma taxa de desconto em custos mais alta reflete o custo de oportunidade das despesas atuais e a preferência temporal pelos recursos. Uma taxa mais baixa de 3% para desfechos é justificada pelo reconhecimento de que a disposição a pagar pela saúde tende a aumentar com o crescimento da renda e as melhorias nos padrões de vida, o que significa que os efeitos futuros sobre a saúde não devem ser desvalorizados tanto quanto os custos financeiros. No contexto da vosoritida, em que melhorias mensuráveis na saúde, como aumento do crescimento, função física e redução de complicações, **acumulam-se anos ou décadas após o início do tratamento**, a aplicação de uma estrutura de 5%/3% garante que esses benefícios futuros para a saúde sejam avaliados de forma adequada em relação aos custos iniciais.

### **Evidência prática e base teórica**

A adoção de 5%/3% é consistente com a experiência em ATS: avaliações de vacinas, como HPV no Reino Unido, mostraram que reduzir a taxa de desconto dos desfechos captura de forma mais adequada benefícios preventivos de longo prazo [136]; em doenças raras, a avaliação do NICE da mifamurtida para osteossarcoma evidenciou que aplicar taxa menor aos benefícios em saúde alterou substancialmente o ICER e a decisão [137]. Do ponto de vista teórico, uma estrutura inspirada no modelo de crescimento ótimo de Ramsey sustenta que, se o valor social da saúde aumenta com renda e disposição a pagar, é apropriado descontar menos os desfechos do que os custos [138].

### **Cenários alternativos**

Em termos de benchmarks, a OMS apresenta 3% para custos e 0% para saúde como caso de referência, além de um cenário 3%/3% [139] e o NICE permite 1,5%/1,5% em condições de longo prazo e alta gravidade [140]. Para a vosoritida na acondroplasia, esses cenários podem ser incluídos como sensibilidade, dado o perfil de custos precoces e benefícios tardios; contudo, o 5%/3% permanece como especificação principal por equilibrar rigor na valoração de recursos e reconhecimento dos ganhos de saúde de horizonte longo.

#### 4.1.4. Estrutura do modelo

Dois estados de saúde: vivo e óbito. Complicações são eventos ocorridos dentro do ciclo no estado “vivo”, com custo agudo e perda de QALY (apenas no ciclo em que ocorrem, sem consequências de longo prazo acumuladas).

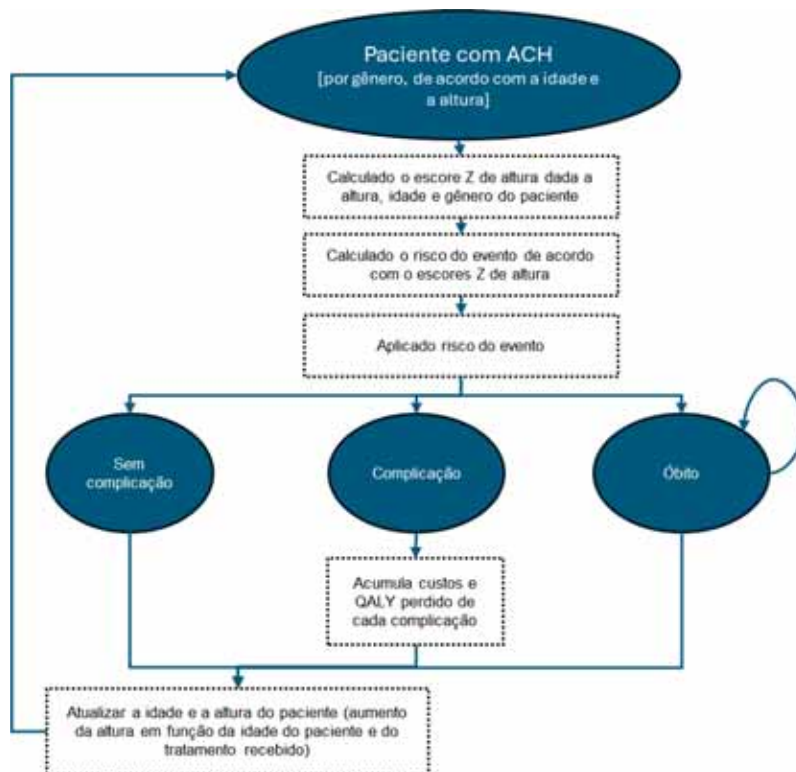
- Mortalidade
  - Cuidado padrão: estudos de história natural;
  - Vosoritida: razão de risco estimada como função do Escore Zde altura (efeito substituto).
- Complicações
  - Cuidado padrão: estudo LIAISE;
  - Vosoritida: redução relativa proporcional ao ganho em Escore Zde altura.
- Antropometria atualizada anualmente.
- Alongamento de membros foi excluído (não realizado no Brasil e não incluído no SUS);
- Cenários com e sem aplicação de desutilidade de cuidadores.

As alternativas comparadas são:

- Vosoritida mais cuidado padrão
- Cuidado padrão apenas, ou seja, manejo das comorbidades e complicações relacionadas à acondroplasia.

A [Figura 28](#) ilustra a estrutura do modelo.

Figura 28. Desenho do modelo



Aos pacientes que apresentam uma complicação são atribuídos custos específicos da complicação e perdas de QALY.

Notas: Linhas sólidas representam estados de saúde e transições entre estados de saúde, por exemplo, de vivo para óbito. Linhas pontilhadas representam eventos que ocorrem durante cada ciclo do modelo, por exemplo, a cada ciclo os pacientes podem experimentar uma complicação (ou não), são atribuídos valores de utilidade baseados na altura e têm suas características (especificamente altura) atualizadas.

#### 4.1.5. Método de modelagem: Crescimento, eficácia e transformação em desfechos

O tratamento impacta VCA e Escore Z de altura, que são os desfechos primários dos estudos clínicos 111-206/208/301/302. O efeito é modelado como a adição da diferença média LS na VCA de vosoritida versus controle por faixa etária, aplicada por ciclo, com escalonamento proporcional em caso de falhas de dose.

Para as curvas de crescimento da população geral, utilizou-se a referência da OMS, conforme recomendação da SBP/MS, considerando que a média é próxima à mediana e que o desvio padrão foi derivado dos percentis por distribuição normal. No caso da acondroplasia, as curvas foram baseadas nos dados do estudo CLARITY e na história natural da coorte controle. Para crianças com menos de 5 anos, adotou-se a história natural, devido à impossibilidade ética de manter placebo por longo período e à



variabilidade e dificuldade de medir comprimento em menores de 6 meses. As diferenças médias LS na VCA (cm/ano) utilizadas no modelo seguem o método mais consistente com os estudos 111-206/301 e suas extensões 111-208/302.

A [Tabela 10](#) abaixo traz as diferenças na VCA entre pacientes tratados com vosoritida e placebo, bem como suas referências.

**Tabela 10. Diferença média dos mínimos quadrados (LS) na velocidade de crescimento anualizada (VCA) nos diferentes estudos**

Idade	Estudo	Horizonte e temporal	Diferença média (95% IC) na VCA entre coortes no modelo (cm/ano)	Fonte
<b>5 a 18 anos</b>	111-301	1 ano	<b>1,57</b> (1,22; 1,93)	<i>Savarirayan 2020 [41]</i>
<b>5 a 18 anos</b> <i>[análise de sensibilidade]</i>	111-302	4 anos	<b>1,64</b> <i>[média ponderada entre 1,84 no sexo masculino e 1,44 no sexo feminino]</i>	<i>Savarirayan 2024 [7]</i>
<b>6 a 24 meses</b>	111-208 (VOS) e história natural (cuidado padrão)	1 ano	<b>2,62</b> (1,40; 3,83)	<i>Data on file</i> (dados do 111-208 [127]; <i>Data on file</i> (pesquisa de história natural)
<b>24 a 60 meses</b>			<b>1,87</b> (1,22; 2,53)	
<b>6 a 24 meses</b>	111-206 (VOS) e história natural (cuidado padrão)	1 ano	2,23 (1,24; 3,22)	<i>Savarirayan 2023 [132]; Data on file</i> (pesquisa de história natural)
<b>24 a 60 meses</b>			1,79 (1,15; 2,44)	
<b>6 a 24 meses</b>	111-206	1 ano	0,63 (-0,6; 1,87)	<i>Savarirayan 2023 [132]</i>
<b>24 a 60 meses</b>			1,10 (0,13; 2,07)	

#### 4.1.6. Qualidade de vida (utilidades)

Na ausência de estudos que quantifiquem utilidade diretamente através de EQ-5D em pediatria de acondroplasia, adotou-se a relação entre utilidade (EQ-5D) e escore Z de altura observada no estudo de Christensen e colaboradores, de 2007 (N=14.416 adultos, Reino Unido) [77].

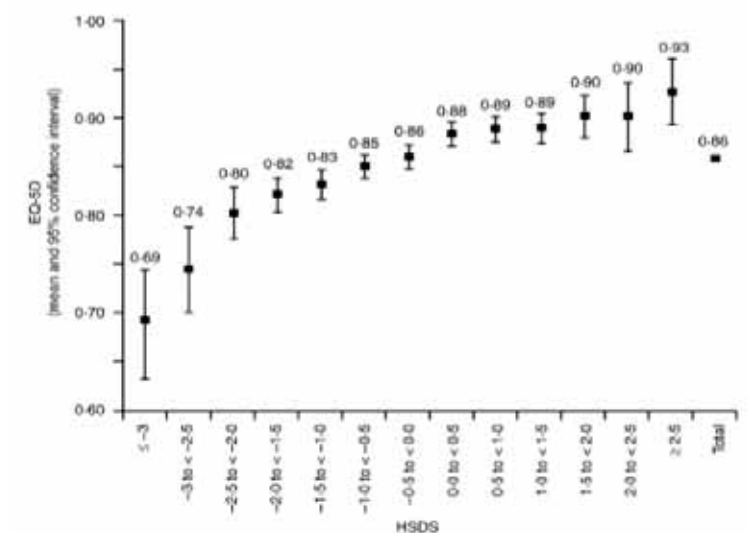
O estudo [79] examinou a influência da altura na qualidade de vida relacionada à saúde para a população adulta geral no Reino Unido. Foi realizada uma pesquisa que registrou informações de 14.836 entrevistas individuais, das quais observações de 14.416 adultos



foram incluídas na análise de qualidade de vida relacionada à saúde. Os valores de utilidade do EQ-5D foram estratificados com base no escore Z da altura dos pacientes, com escores Z negativos maiores associados a uma utilidade reduzida, como ilustrado na [Figura 29](#).

Para valores de Z inferiores a -3, comuns em acondroplasia, foi necessária extrapolação por regressão polinomial quadrática, método escolhido e validado por um painel de especialistas, incluindo endocrinopediatra brasileiro, por melhor representar tendências e platôs. Observa-se que o EQ-5D apresenta menor sensibilidade que o QoLISSY para capturar incrementos de altura, tornando o modelo conservador; além disso, análises de DCE sugerem um paradoxo da deficiência no EQ-5D, possivelmente subestimando o impacto na QVRS. Considerou-se ainda um incremento absoluto adicional de 0,1 na utilidade ao atingir 150 cm, limiar funcional associado a maior alcance e mobilidade independente.

**Figura 29. Valores de utilidade com base na altura relatados em Christensen, 2007 [79]**

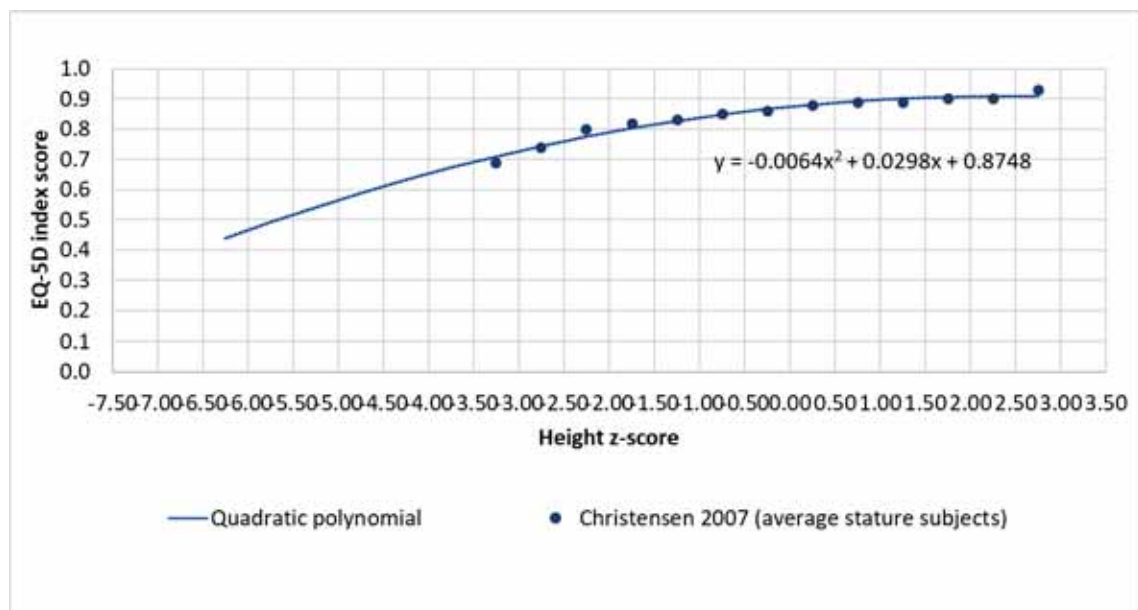


Conforme ilustrado na [Figura 30](#), os dados de utilidade do estudo de Christensen [79] são extrapolados para permitir a estimativa de valores de utilidade associados ao escore Z de altura além dos intervalos relatados no estudo. Isso é necessário, pois os pacientes com acondroplasia geralmente têm escore Z de altura abaixo de -3, enquanto o estudo [79] não estratifica pacientes com escore Z de altura abaixo de -3.

Médicos especialistas, incluindo um endocrinologista pediátrico brasileiro, foram consultados e concordaram que os dados deste estudo [79] poderiam ser extrapolados para pacientes com acondroplasia, inclusive, observou-se que, ao usar dados da população geral (sem a inclusão de baixa estatura desproporcional), o efeito do aumento da altura na QVRS em pessoas com acondroplasia pode ser subestimado.

Também foi considerado que a regressão polinomial quadrática era o método mais apropriado para extrapolar os dados do estudo de Christensen [79], porque considera tendências e platôs e é uma melhor representação da relação entre o escore Z de altura e a QVRS na prática clínica. Portanto, uma função de regressão polinomial quadrática foi aplicada para ajustar os dados do ensaio e fornecer estimativas de utilidade extrapoladas plausíveis para pacientes com escore Z de altura abaixo de -3.

**Figura 30. Extrapolação dos valores de utilidade baseados na altura de Christensen, 2007 [79]**



Observa-se que o uso dos dados deste estudo [79] para informar os valores de utilidade é consistente com outras duas avaliações econômicas publicadas em populações de baixa estatura (Christensen 2010 e Takeda 2010) [79, 141]. A principal diferença entre as utilidades aplicadas nesses estudos e as aplicadas no modelo econômico atual relaciona-se à extrapolação dos dados do estudo [79]. Em contraste, os escores Z de altura de linha de base nestes dois estudos eram muito próximos da curva do estudo original (não ultrapassando o limite inferior da amostra de -3,0), fazendo com que não houvesse a necessidade de extrapolar os dados de Christensen nestes casos.



É importante notar também que o instrumento EQ-5D pode não ser tão sensível ao impacto do escore Z da altura na qualidade de vida em comparação com outros instrumentos de qualidade de vida relacionada a saúde, como o QoLISSY, que demonstrou a correlação mais significativa entre as medidas de qualidade de vida relacionada à saúde e o escore Z da altura na análise do LIAISE [78]. Portanto, pose-se considerar que este modelo é conservador quanto ao impacto positivo em utilidade do ganho de altura, uma vez que o EQ-5D é menos sensível aos incrementos graduais. Além disso, um estudo Experiência de Escolha Discreta (DCE na sigla em inglês) detectou a presença de um paradoxo da deficiência nas medidas do EQ-5D em sujeitos com acondroplasia, o que sugere que o impacto da acondroplasia pode ser subestimado se comparado aos conjuntos de valores da população geral existentes para o EQ-5D-5L.

### **Desutilidade de cuidadores**

A acondroplasia impõe uma carga substancial e contínua aos cuidadores, decorrente da necessidade de acompanhamento frequente, suporte em atividades da vida diária e manejo de complicações clínicas. Essa carga se traduz em perdas mensuráveis de qualidade de vida, reconhecidas na literatura e refletidas em parâmetros de utilidade. A não consideração dessas desutilidades no caso base resultaria em subestimação dos impactos reais da condição e, conseqüentemente, dos benefícios proporcionados por intervenções que reduzem a dependência e a intensidade do cuidado ao longo do tempo. A inclusão da desutilidade de cuidadores, portanto, assegura que a análise de custo-utilidade capture de forma mais abrangente o efeito da tecnologia sobre o bem-estar global, alinhando-se às boas práticas internacionais e à perspectiva social implícita nas diretrizes nacionais.

O valor de desutilidade atribuído à categoria “ $-3 < \text{Escore Z}$ ” foi ajustado para corresponder ao da categoria “ $-4 < \text{Escore Z} \leq -3$ ”. Essa decisão se deve ao fato de que o valor originalmente observado para “ $-3 < \text{Escore Z}$ ” indicava, de forma pouco plausível, um impacto muito maior sobre o cuidador do que em categorias de altura mais graves, o que carece de validade aparente. Além disso, esse valor baseava-se em apenas uma observação e destoava da tendência consistente identificada nas demais categorias de escore Z. A imputação do mesmo valor da categoria adjacente assegura coerência na relação entre gravidade e desutilidade, evitando distorções decorrentes de dados isolados e garantindo maior robustez ao modelo.

#### 4.1.7. Complicações

Complicações entram como eventos de ciclo com custo agudo [142] e desutilidade aplicada no ciclo corrente [143, 144]. A redução de complicações no braço vosoritida é uma função do escore Z (razão idêntica à relação de utilidade de Christensen 2007 [79]).

Complicações incluídas: estenose de forame magno, hidrocefalia, apneia do sono, estenose espinhal, cifose, arqueamento das pernas, doença cardiovascular, otite média, má oclusão dentária.

A Tabela 33, no ANEXO II, traz um resumo das complicações, procedimentos, códigos SIH e custos incluídos.

#### 4.1.8. Custos (vosoritida, eventos, monitoramento)

##### ***Vosoritida***

A dosagem baseada em faixas de peso é recomendada para vosoritida com base em uma dose usual de 30 µg/kg para pacientes com menos de dois anos de idade e 15 µg/kg para pacientes com dois anos ou mais. Para isso, estão disponíveis três apresentações 0,4 mg (0,8 mg/mL), 0,56 mg (0,8 mg/mL) e 1,2 mg (2 mg/mL).

O preço de vosoritida é o mesmo independentemente da apresentação. O PMVG sem impostos por frasco é de R\$ 3.105,89. A BioMarin propõe um desconto comercial de 20,0% em relação ao preço PMVG sem impostos para a incorporação, resultando no valor unitário de R\$ 2.484,71.

Recomenda-se que seja administrado como uma injeção diária, assim um paciente totalmente em conformidade receberia uma estimativa de 365 doses por ano. Assume-se que as injeções de vosoritida são autoadministradas pelo paciente, ou administradas por um cuidador, e como tal estão associadas a zero custos de administração. Também foi incluída uma taxa de aderência de 92,5%, com base nos estudos de mundo real (RWE), além de uma taxa anual de descontinuação de 2,9% que é segundo o estudo 205.

A Tabela 11 apresenta o custo de tratamento anual considerado no modelo.

**Tabela 11. Custo de tratamento por ciclo (ano)**

Preço PMVG sem impostos por frasco	R\$ 3.105,89
Desconto comercial em relação ao preço PMVG sem impostos por frasco	20,0%
Preço com desconto*	R\$ 2.484,71
Quantidade de frascos anuais	365
Taxa de aderência	92,5%
Custo anual	R\$ 839.475,75

\*Preço para fins referenciais apenas

### ***Custo das complicações***

Conforme mencionado, as complicações estão incluídas no modelo. Um custo de evento agudo é aplicado no modelo para o tratamento dessas complicações. A [Tabela 33, no ANEXO II](#), fornece um resumo das intervenções assumidas para o tratamento das complicações incluídas. Os custos dos eventos aplicáveis a cada intervenção são posteriormente derivados de consulta ao SIH para o período de 2023. A definição dos procedimentos relacionados a cada complicação foi validada por médicos especialistas brasileiros

### ***Eventos adversos***

Vosoritida é bem tolerada em comparação com o cuidado padrão, com as únicas diferenças observadas entre vosoritida e nenhum tratamento (ou seja, placebo) relacionadas ao modo de administração (reações no local da injeção, inchaço no local da injeção), com eventos geralmente leves em gravidade. Dado o perfil de segurança tolerável da vosoritida, nenhum custo relacionado a eventos adversos do medicamento é incorporado no modelo.

### ***Custo de monitoramento***

Os pacientes tratados com vosoritida têm requisitos de monitoramento contínuo semelhantes aos daqueles gerenciados com cuidado padrão. Nesse sentido, as diferenças no monitoramento esperado para pacientes tratados com vosoritida versus aqueles gerenciados com cuidado padrão espera-se que sejam mínimas e, portanto, os custos de monitoramento não estão incluídos no modelo econômico.



#### 4.1.9. Premissas do modelo

As premissas assumidas para cada parâmetro do modelo de custo-utilidade estão descritas na

Tabela 12.

**Tabela 12. Premissas do modelo de custo-utilidade**

Parâmetros	Descrição no modelo	Input	Referência
Horizonte temporal	Intervalo de 0 até a vida inteira (101 anos), o modelo assume 100% de mortalidade quando os pacientes atingem 101 anos de idade	<i>Lifetime</i>	Como menciona no Manual de Avaliação Econômica do Ministério da Saúde, o horizonte temporal deve tomar como base, o curso natural da condição mórbida e o provável impacto que a intervenção tenha sobre ele, devendo ser capaz de capturar todas as consequências e custos relevantes para a medida de resultado escolhida. Em doenças crônicas ou com desfechos em longo prazo, a não ser que haja justificativa clara para outro horizonte, prioritariamente se deve adotar a expectativa de vida dos pacientes como horizonte temporal.
Taxa de desconto – custos (cenário base)	A taxa de desconto a ser aplicada em custos	5%	<i>Guideline Brasileira de Modelos Econômicos em Saúde</i>



Taxa de desconto – desfechos (cenário base)	A taxa de desconto a ser aplicada em QALYs e LYs	3%	
Correção de meio ciclo	Aplicado		Guideline Brasileira de Modelos Econômicos em Saúde
Idade de início da terapia	Os pacientes iniciam com 6 meses de idade, conforme definição em bula.	0,5 ano	Bula do produto
Idade de parada da terapia	Idade em que o tratamento não será mais administrado. O último ano de tratamento é o ano anterior a esse valor.	15 anos para meninas e 17 anos para meninos	Premissa com base nas tabelas de altura populacional, refletindo as idades com crescimento < 1,5 cm/ano
Custo da vorosítida	Custo anual com base na quantidade de unidades consumidas por anos	PMVG sem impostos com 20,0% de desconto	Cálculo BioMarin
Gênero, masculino	A distribuição de gênero com base na suposição de prevalência masculina.	50,6%	Estimativa de pacientes brasileiros do sexo masculino para o ano de 2025, com base nas informações do modelo de impacto orçamentário
Percentil de altura	As entradas de percentil de altura são selecionadas aleatoriamente para as coortes		Premissa
Conjunto de dados de altura - população geral	Gráfico da OMS		Recomendado pelo Ministério da Saúde e pela Sociedade Brasileira de Pediatria
Conjunto de dados de altura – população com acondroplasia	CLARITY		Recomendado pela Sociedade Brasileira de Pediatria
Tabua de mortalidade	Tabua de mortalidade segundo IBGE		IBGE



Diferença média na VCA >5 anos	Dados de eficácia do estudo clínico pivotal de fase III. Cenário base vem da fase randomizada, controlada (301) e cenário alternativo vem da publicação com 4 anos de dados da fase de extensão (302)	111-301; 111-302
Diferença média na VCA 0 a < 2 anos; e >= 2 a <5 anos	A análise comparativa detalhada no relatório de história natural, em que os dados do estudo 111-208 informam que a VCA no braço da vosoritida e a VCA no braço do placebo são derivados de um conjunto de dados de história natural (2,62 [1,4, 3,83]; 1,87 [1,22, 2,53])	Melhor dado disponível de comparação para este subgrupo de faixa etária, devido à impossibilidade de manutenção do placebo no estudo 111-208.
Probabilidade anual de descontinuação do tratamento	2,9%	Baseada no estudo 111-205 (n=30; duração média de 57,77 meses).
Razão de mortalidade padronizada (ACH vs. população geral) - elevada durante a infância	6 A mortalidade elevada é modelada durante a infância para levar em conta a morte súbita, comumente atribuída à estenose do forame magno	Simmons 2014 [56]
Razão de mortalidade padronizada (ACH vs. população geral) - padrão pós-infância	Após esse período de mortalidade elevada, é aplicada uma razão padrão	Premissa
Período de elevação Razão de mortalidade padronizada (ACH vs. população geral) - idade	0 a 1 ano de idade; a mortalidade elevada é modelada durante a infância para levar em conta a morte súbita, comumente atribuída à estenose do forame magno	Premissa



Mortalidade - benefício do tratamento	Riscos de mortalidade para vosoritida estimados com base no escore Z de altura	Morgan 2024 [145]
Regressão de utilidade	Polinômio quadrático	Opinião de especialistas
Limite de altura (cm) para aumento absoluto na utilidade	150	Este incremento é assumido devido ao atingimento da capacidade de alcançar objetos e se movimentar de forma independente e sem auxílios o apoio ao cruzar esse limiar, ou seja, evitando o impacto da deficiência associada à baixa estatura.
Aumento absoluto ao atingir o limite de altura (utilidade)	0,1	
Complicações - benefício do tratamento	Riscos de redução de complicação para vosoritida estimados com base no escore Z de altura	A razão de redução de complicações foi assumida como sendo a mesma razão de melhoria de qualidade de vida observada em Christensen 2007 [79]
Custo do evento de complicações	Estenose do forame magno, hidrocefalia, apneia do sono, estenose espinhal, cifose, arqueamento das pernas, doença cardiovascular, otite média, má oclusão dentária	Custo do DATASUS com base nos procedimentos descritos por especialistas locais
Desutilidade do cuidador	Essa variável pode ser escolhida pelo uso. O caso base aplica um valor que é derivado da literatura e é aplicável a várias jurisdições.	Due 2024 [75]



Desutilidades de eventos de complicações	de	Desutilidades de eventos para: Estenose do forame magno, hidrocefalia, apneia do sono, estenose espinhal, cifose, arqueamento das pernas, doença cardiovascular, otite média, má oclusão dentária	Sullivan 2011 [143]
Desutilidades de eventos de complicações	de	Desutilidades por faixa de escore Z de altura	Kuhlthau 2010 [144]

#### 4.1.10. Métodos analíticos de apoio

Foram realizadas análises de sensibilidade determinística e probabilística, conforme detalhado na Tabela 34, no ANEXO II.

### 4.2 Resultados

#### 4.2.1 Caso base

Na comparação entre vosoritida e cuidado padrão, o tratamento com vosoritida resultou no ganho de 18,7 anos de vida ajustados pela qualidade (QALYs), contra 12,4 QALYs com cuidado padrão, refletindo em um ganho incremental de 6,3 QALYs. O custo incremental do uso de vosoritida foi de R\$ 7.017.615. A razão de custo-efetividade incremental (RCEI) foi estimada em R\$ 1.115.592 por QALY ganho. Incluindo o desutilidade do cuidador (componente societário), o RCEI foi estimado em R\$ 846.638/QALY.

**Tabela 13. Resultado caso base**

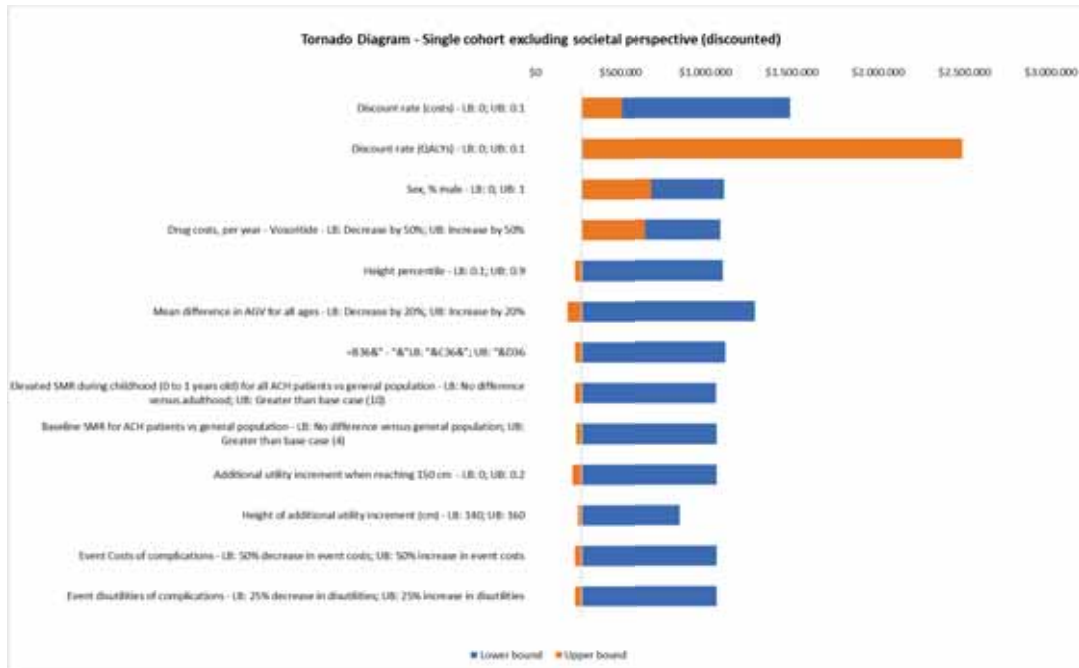
	Vosoritida	Cuidado padrão	Incremental
QALYs	18,7	12,4	6,3
Custo total	R\$ 6.686.704,48	R\$ 2.263	R\$ 6.684.441,53
RCEI (sem componente societário)	R\$ 1.062.627,18		
RCEI (com componente societário)	R\$ 846.638		

No Brasil, a taxa de desconto recomendada para avaliações econômicas de tecnologias de saúde é de 5%. Essa taxa de desconto tem um impacto significativo no QALY incremental, ao longo do tempo. No caso da vosoritida, que é um tratamento limitado no tempo, mas com benefício para a vida toda, isto é especialmente relevante. Por isso, o caso base apresentado considerou desconto de 5% nos custos e de 3% nos desfechos. O incremento de QALYs sem a aplicação do desconto foi de 18,4, enquanto com a aplicação do desconto de 5% em custos e desfechos, o valor foi reduzido para 3,8 QALYs adicionais. No cenário sem aplicação de taxa de desconto a RCEI seria 52% menor (R\$ 508.504).

### 4.2.2 Análises de Sensibilidade univariada

A Figura 31 mostra que as variáveis que mais impactaram o modelo na comparação entre vosoritida e cuidado padrão foram os custos de aquisição de vosoritida por ano, a taxa de desconto nos QALYs, a proporção de pacientes do sexo masculino, a diferença média na VCA e a taxa de desconto nos custos.

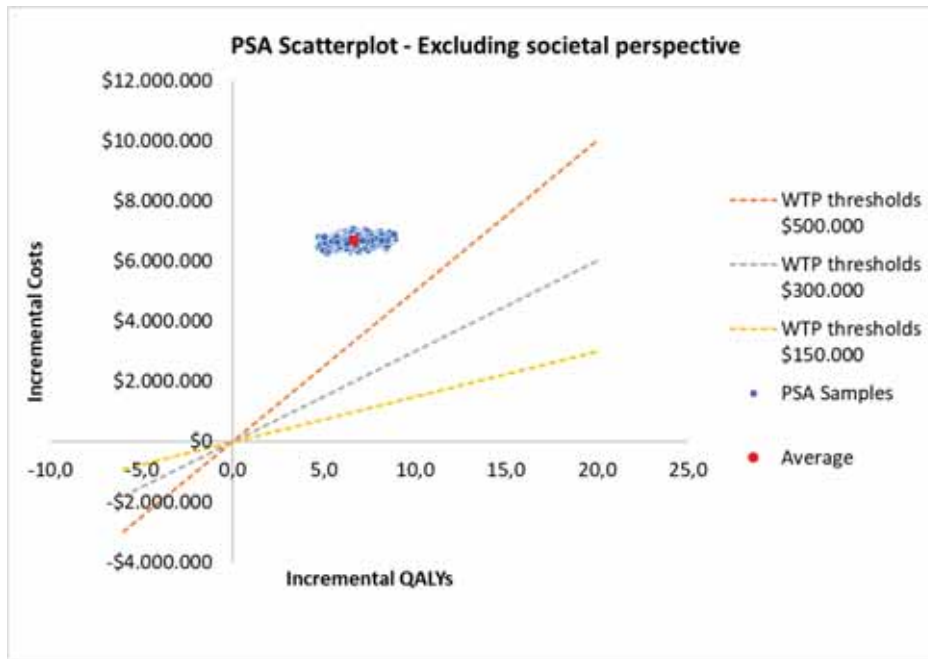
**Figura 31. Análise de sensibilidade determinística para o desfecho QALY**



### 4.2.3 Análises de Sensibilidade probabilística

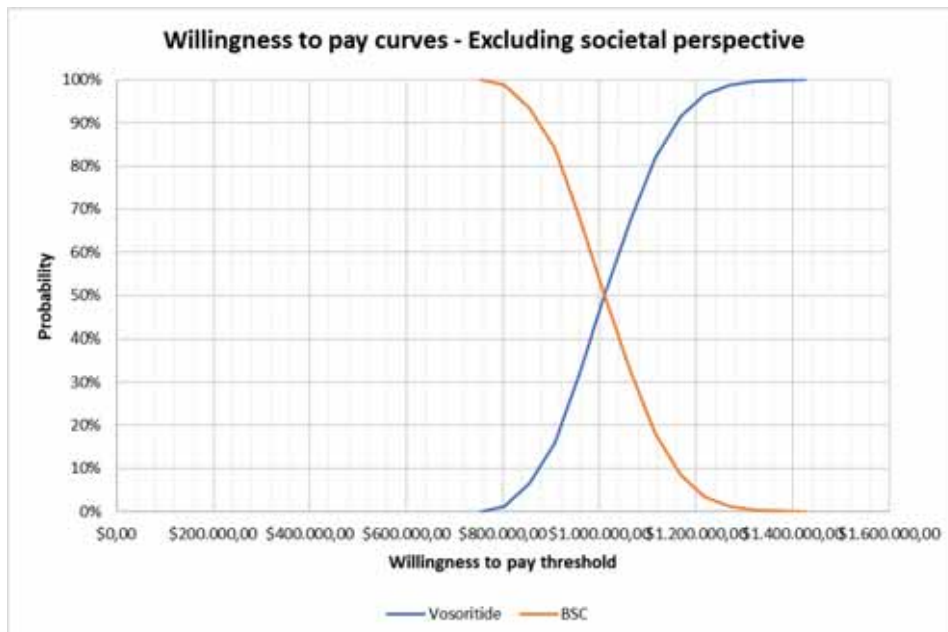
Na PSA, os resultados se mantiveram consistentes com o caso-base. Na comparação entre vosoritida e cuidado padrão, a RCEI média das 1.000 iterações foi R\$ 1.615.708 /QALY. O custo incremental médio foi R\$ 3.975.210, e a efetividade incremental média foi de 2,46 QALY. Em 100% das iterações, o resultado se encontra no quadrante I (maior custo e maior efetividade incremental), mostrando que o tratamento com vosoritida é associado a maiores custos, mas atinge maiores benefícios em saúde do que o Cuidado padrão.

**Figura 32. Análise de sensibilidade probabilística com 1.000 iterações**



Os resultados da análise de sensibilidade probabilística também são ilustrados pela curva de aceitabilidade de custo-efetividade, que define a probabilidade de uma tecnologia ser custo-efetiva dependendo de um limiar específico de disposição a pagar, que é o limiar de custo-efetividade incremental (RCEI).

**Figura 33. Curva de aceitabilidade de custo-efetividade, vosoritida vs. Cuidado padrão**



## 5. IMPACTO ORÇAMENTÁRIO

A presente análise de impacto orçamentário (AIO) foi desenvolvida com o intuito de simular o impacto financeiro da incorporação da vosoritida para o tratamento de pacientes com acondroplasia a partir de 6 meses de idade e cujas epífises não estão fechadas.

### 5.1. Métodos

#### 5.1.4. Definição da população

Foreman e colaboradores (2020) realizaram uma metanálise que estimou a prevalência média de acondroplasia no nascimento [3]. As estimativas para a prevalência média de acondroplasia no nascimento na América Latina variam de 1,64 a 4,75 por 100.000 nascimentos, de acordo com cinco estudos separados conduzidos entre 1991 e 2018, com uma média de 3,2 por 100.000 nascimentos. A estimativa da população prevalente com acondroplasia para o ano 1 (2026) com idade menor que 18 anos está apresentada na [Tabela 35, no ANEXO II](#).



Para os anos subsequentes foi calculada a incidência com base na projeção de nascidos vivos no Brasil segundo IBGE (*Tabela 35, no ANEXO II*).

Foram aplicados os seguintes restritores:

- % de pacientes com 0 (zero) anos de idade elegíveis: ajuste de 50% para refletir que a indicação em bula do produto é a partir de 6 meses de idade.
- % de pacientes com epífise aberta (meninos): assumindo como 17 anos. Esta premissa foi validada com base na curva de crescimento da OMS, determinando a idade em que um adolescente apresenta um crescimento inferior a 1,5 cm no período de um ano, uma vez que este é o critério de interrupção do tratamento conforme bula aprovada pela ANVISA.
- % de pacientes com epífise aberta (meninas): assumindo como 15 anos. Esta informação foi validada com base na curva de crescimento da OMS, determinando a idade em que um adolescente apresenta um crescimento inferior a 1,5 cm no período de um ano, uma vez que este é o critério de interrupção do tratamento conforme bula aprovada pela ANVISA.
- % taxa de acesso ao centro de referência ou especialista habilitado: foi estimado com base na distribuição das apresentações vendidas de vosoritida, que reflete o peso e, indiretamente, a idade dos pacientes brasileiros tratados, em comparação com a prevalência estimada pela epidemiologia. No ano 1, foi estimado em 100% para pacientes entre 0 e 5 anos, 75% entre 6 e 9 anos e 50% a partir de 10 anos. Nos anos subsequentes, as taxas menores são carregadas para idades de  $n+1$ . Esta distribuição reflete a menor taxa de busca por serviços médicos especializados em famílias de pacientes mais velhos que não iniciaram tratamento anteriormente. Se assume que será necessário ter acesso a um especialista habilitado ou a um centro de referência para que seja feita a confirmação genética do diagnóstico e a subsequente prescrição da vosoritida, configurando-se como uma limitação estrutural do sistema, pois implica que pacientes sem este acesso não estarão elegíveis ao tratamento.

Com isso, a quantidade de pacientes elegíveis por idade em cada um dos anos avaliados está apresentada na *Tabela 14*.

**Tabela 14. Pacientes elegíveis por idade**

Idade	2026	2027	2028	2029	2030
0	45	45	44	44	43
1	84	90	89	88	87
2	74	84	90	89	88
3	75	74	84	90	89
4	78	75	74	84	90
5	80	78	75	74	84
6	62	80	78	75	74
7	65	62	80	78	75
8	64	65	62	80	78
9	63	64	65	62	80
10	44	63	64	65	62
11	43	44	63	64	65
12	42	43	44	63	64
13	42	42	43	44	63
14	42	42	42	43	44
15	42	42	42	42	43
16	21	21	22	21	21
17	22	21	21	22	21
18	0	0	0	0	0

### 5.1.5. Tecnologias consideradas

#### *Descrição do cenário atual*

Conforme mencionado anteriormente, até o presente momento não existem tratamentos incorporados no SUS para a acondroplasia. O atual manejo da acondroplasia se concentra na atenuação dos sintomas e complicações, exigindo vários procedimentos invasivos, medicamentos e intervenções comportamentais/ambientais, bem como supervisão cuidadosa.

#### *Descrição do cenário proposto*

O cenário proposto é composto por vosoritida e cuidado padrão.

Estima-se que 389 pacientes sejam tratados com vosoritida no primeiro ano, distribuídos por idade conforme o cálculo de incidência. Este número foi obtido através de pedido de



acesso à informação<sup>1</sup> realizado pela BioMarin ao Ministério da Saúde, através da Lei 12.527/2011 (“Lei de Acesso à Informação”).

A participação de mercado no primeiro ano foi calculada com base na premissa de quantidade de pacientes tratados (389), em relação à população elegível estimada. A partir desta premissa, se assume que nos anos seguintes a participação de mercado crescerá gradualmente atingindo o valor máximo de participação de mercado de 75% no quinto ano. A [Tabela 15](#) apresenta a participação de mercado estimada no cenário base.

**Tabela 15. Participação de mercado (*market share*)**

	2026	2027	2028	2029	2030
Vosoritida	39,4%	45%	55%	65%	75%
Cuidado padrão	60,6%	55%	45%	35%	25%

### 5.1.6. Perspectiva da análise

A perspectiva em análise é a do SUS.

### 5.1.7. Horizonte temporal da análise

Adotou-se um horizonte temporal de 5 anos (2026 a 2030), conforme recomenda a Diretriz para Análise de Impacto Orçamentário.

### 5.1.8. Custos

Foi decidido não considerar no modelo custos devido as complicações incidentes ou evitadas pelo tratamento, devido à maior complexidade que levaria a um grau de incerteza maior. Uma vez que, conforme discutido no modelo de custo-utilidade, é esperado que o tratamento com vosoritida reduza a incidência de complicações, pode-

<sup>1</sup> Conforme resposta enviada no dia 25/08/2025 ao pedido de acesso à informação realizado pela BioMarin ao Ministério da Saúde, através da Lei 12.527/2011 (“Lei de Acesso à Informação”), existem 389 pacientes com tratamento ativo, 60 com processos suspensos e 54 em fase de subsídios. Consideramos apenas os ativos como premissa de pacientes que acessariam o tratamento por vias administrativas no primeiro ano da incorporação efetiva.



se afirmar que esta simplificação da AIO também a torna mais conservadora, ou seja, demonstra custos provavelmente acima do esperado.

A dosagem baseada em faixas de peso é recomendada para vosoritida com base em uma dose usual de 30 µg/kg para pacientes com menos de dois anos de idade e 15 µg/kg para pacientes com dois anos ou mais. Para isso, estão disponíveis três apresentações 0,4 mg (0,8 mg/mL), 0,56 mg (0,8 mg/mL) e 1,2 mg (2 mg/mL).

O preço de vosoritida é o mesmo independentemente da apresentação. Um preço PMVG sem impostos por frasco é de R\$ 3.105,89. A BioMarin propõe um desconto comercial de 20,0% em relação ao preço PMVG sem impostos, resultando no valor unitário de R\$ 2.484,71.

Recomenda-se que seja administrado como uma injeção diária, assim um paciente totalmente em conformidade receberia uma estimativa de 365 doses por ano. Devido ao uso em ambiente domiciliar, assume-se que as injeções de vosoritida são autoadministradas pelo paciente, ou administradas por um cuidador, e como tal estão associadas a zero custos de administração. Também foi incluída uma taxa de aderência de 92,5%, segundo estudos de mundo real, além de uma taxa anual de descontinuação de 2,90% que é segundo o estudo 111-205.

A [Tabela 16](#) apresenta o custo de tratamento anual considerado no modelo.

**Tabela 16. Custo de tratamento por ano**

Preço PMVG sem impostos por frasco	R\$ 3.105,89
Desconto comercial em relação ao preço PMVG sem impostos por frasco	20,0%
Preço com desconto*	R\$ 2.484,71
Quantidade de frascos anuais	365
Taxa de aderência	92,5%
Custo anual	R\$ 838.901,16

**\*Preço para fins referenciais apenas. Vide Considerações Gerais na Seção 7**

### 5.1.9. Análise de sensibilidade

Foi realizada uma análise de sensibilidade modificando, para baixo e para cima, o máximo de participação de mercado, resultando nos cenários alternativos 1 e 2.

No “cenário alternativo 1”, a participação de mercado foi alterada para 60% no último ano, a fim de se refletir possíveis dificuldades no acesso ao diagnóstico ou aos



especialistas aptos a prescrever o tratamento com vosoritida. Com isso a participação de mercado seria conforme a Tabela 17. A premissa de 60% de participação de mercado está alinhada com o observado em outras submissões de decisões da CONITEC para tecnologias em doenças raras, uma vez que reflete os conhecidos desafios existentes na jornada terapêutica destes pacientes, desde a confirmação do diagnóstico até a consulta com o especialista adequado que efetivamente prescreve o tratamento.

**Tabela 17. Participação de mercado – Cenário alternativo 1**

	2025	2026	2027	2028	2029
Vosoritida	39,4%	40%	45%	50%	60%
Cuidado padrão	60,6%	60%	55%	50%	40%

No “cenário alternativo 2”, a participação de mercado foi alterada para 80% no último ano, simulando um cenário de rápida difusão da tecnologia pelo sistema, assumindo que a jornada dos pacientes até os médicos prescritores tenha sido facilitada por fluxos de encaminhamento, e o que médicos tenham alta aceitação e disposição a prescrever a tecnologia. A participação de mercado resultante deste cenário encontra-se na [Tabela 18](#).

**Tabela 18. Participação de mercado – Cenário alternativo 2**

	2025	2026	2027	2028	2029
Vosoritida	28,4%	35%	50%	65%	80%
Cuidado padrão	71,6%	65%	50%	35%	20%

## 5.2. Resultados

### 5.2.1. Caso base

A [Tabela 19](#) apresenta a quantidade de pacientes em tratamento em cada um dos anos avaliados, chegando a 846 pacientes em tratamento com vosoritida no último ano. Conforme apresentado na [Tabela 20](#), o impacto orçamentário gerado para tratar 816 pacientes ao longo de 5 anos é de R\$ 2.400.515.667.

**Tabela 19. Número total de pacientes em terapia**

	2026	2027	2028	2029	2030
<b>Cenário atual - Cuidado padrão</b>	988	1.035	1.082	1.128	1.171
<b>Cenário proposto - Vosoritida</b>	392	453	570	692	816
<b>Cenário proposto - Cuidado padrão</b>	596	582	512	436	355

**Tabela 20. Impacto orçamentário em 5 anos**

	2026	2027	2028	2029	2030	Em 5 anos
<b>Cenário atual - Cuidado padrão</b>	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0
<b>Cenário proposto - Vosoritida + Cuidado Padrão</b>	R\$ 321.299.144	R\$ 371.633.213	R\$ 468.106.847	R\$ 568.355.535	R\$ 671.120.927	R\$ 2.400.515.667
<b>Impacto orçamentário</b>	R\$ 321.299.144	R\$ 371.633.213	R\$ 468.106.847	R\$ 568.355.535	R\$ 671.120.927	R\$ 2.400.515.667

## 5.2.2. Análise de sensibilidade

### Cenário alternativo 1

A análise de sensibilidade realizada no “cenário alternativo 1” considera um cenário com uma maior dificuldade de os pacientes acessarem a terapia e, portanto, uma menor participação de mercado. Ao final de 5 anos, seriam 650 pacientes tratados com vosoritida gerando um impacto orçamentário de R\$ 1.995.745.857.

**Tabela 21. Número total de pacientes em terapia – Cenário alternativo 1**

	2026	2027	2028	2029	2030
<b>Cenário atual - Cuidado padrão</b>	988	1.035	1.082	1.128	1.171
<b>Cenário proposto - Vosoritida</b>	392	401	463	525	650
<b>Cenário proposto - Cuidado padrão</b>	596	634	619	603	521



**Tabela 22. Impacto orçamentário em 5 anos – Cenário alternativo 1**

	2026	2027	2028	2029	2030	Em 5 anos
<b>Cenário atual - Cuidado padrão</b>	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0
<b>Cenário proposto - Vosoritida + Cuidado Padrão</b>	R\$ 321.299.144	R\$ 328.849.254	R\$ 380.022.225	R\$ 431.195.196	R\$ 534.380.038	R\$ 1.995.745.857
<b>Impacto orçamentário</b>	R\$ 321.299.144	R\$ 328.849.254	R\$ 380.022.225	R\$ 431.195.196	R\$ 534.380.038	R\$ 1.995.745.857

Cenário alternativo 2

O “cenário alternativo 2” considera que os pacientes encontrem mais facilidade de acesso aos centros de referência para prescrição da terapia e, portanto, uma maior participação de mercado da vosoritida. Ao final de 5 anos, seriam 1.039 pacientes tratados com vosoritida gerando um impacto orçamentário de R\$ 2.822.902.400.

**Tabela 23. Número total de pacientes em terapia – Cenário alternativo 2**

	2026	2027	2028	2029	2030
<b>Cenário atual - Cuidado padrão</b>	1.371	1.377	1.381	1.385	1.386
<b>Cenário proposto - Vosoritida</b>	390	470	667	856	1.039
<b>Cenário proposto - Cuidado padrão</b>	981	907	714	529	347

**Tabela 24. Impacto orçamentário em 5 anos – Cenário alternativo 2**

	2026	2027	2028	2029	2030	Em 5 anos
<b>Cenário atual - Cuidado padrão</b>	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0	R\$ 0
<b>Cenário proposto - Vosoritida + Cuidado Padrão</b>	R\$ 321.718.595	R\$ 387.572.336	R\$ 550.319.160	R\$ 705.935.325	R\$ 857.356.985	R\$ 2.822.902.400
<b>Impacto orçamentário</b>	R\$ 321.718.595	R\$ 387.572.336	R\$ 550.319.160	R\$ 705.935.325	R\$ 857.356.985	R\$ 2.822.902.400

## 6. RECOMENDAÇÕES DE AGÊNCIAS DE ATS

A vosoritida já foi incorporada ou recebeu recomendação positiva de agências de avaliação de tecnologias em saúde (ATS) em diversos países, incluindo:

- **França** (HAS, 2021): Recomendação positiva para pacientes  $\geq 2$  anos, reconhecendo alta necessidade médica não atendida e benefício clínico significativo.
- **Alemanha** (G-BA, 2024): Avaliação positiva para pacientes  $\geq 4$  meses, com benefício adicional imensurável ou não quantificável.
- **Austrália** (PBAC, 2022): Recomendação positiva a partir do nascimento, reconhecendo valor terapêutico agregado e necessidade clínica urgente.
- **Espanha** (AEMPS, 2024): Primeira escolha para pacientes pediátricos, com benefício clínico e perfil de segurança razoável.
- **Itália** (AIFA, 2022): Recomendação positiva para pacientes  $\geq 2$  anos.
- **Polônia** (AOTMiT, 2024): Recomendação positiva, reconhecendo benefício em parâmetros de crescimento e potencial impacto positivo na qualidade de vida.

As decisões internacionais reforçam a robustez das evidências clínicas e a relevância da vosoritida como padrão ouro para o tratamento etiológico da acondroplasia.

A [Tabela 37, no ANEXO II](#), apresenta a lista completa recomendações de incorporação de vosoritida globalmente, incluindo populações cobertas e justificativas.

## 7. CONSIDERAÇÕES FINAIS

### Vosoritida: Mudança de paradigma no manejo da Acondroplasia

A **vosoritida** representa uma **mudança de paradigma** no tratamento da acondroplasia, com benefícios **clínicos, funcionais, psicossociais e econômicos** comprovados em ensaios clínicos robustos, extensões de longo prazo e dados de vida real, incluindo coortes brasileiras [7, 40-42, 44-47, 133, 146]. Sua incorporação ao SUS tem potencial para:

- **Aumentar independência funcional e qualidade de vida** das novas gerações de crianças com acondroplasia, permitindo que se tornem adultos mais saudáveis;
- **Reduzir complicações graves e a carga associada;**
- **Diminuir ônus econômico e social**, promovendo **equidade e inclusão;**
- **Melhorar altura e proporcionalidade corporal** de forma sustentada.

### Acondroplasia: Impacto Clínico e Social

A acondroplasia é uma **doença genética rara, autossômica dominante e progressiva**, causada por mutação no **FGFR3**, que inibe a ossificação endocondral. Afeta cerca de **250 mil pessoas no mundo** e **~7.600 no Brasil** (1.500 <18 anos), com prevalência de **3,2/100.000 nascidos vivos**. A altura final média é de **124 cm (mulheres)** e **133 cm (homens)** [1, 3, 19].

Além da baixa estatura, há **complicações ortopédicas, neurológicas, respiratórias e metabólicas**, levando a dor crônica, perda funcional e expectativa de vida **10 anos menor**. O risco de morte súbita no 1º ano pode chegar a **7,5%**, principalmente por estenose do forame magno [1, 57]. A QVRS é significativamente reduzida, com impacto físico, social e emocional [4, 5, 24]. **Melhorar a altura e a proporcionalidade correlaciona-se diretamente com ganhos funcionais e psicossociais** [6, 63].

Socialmente, a doença impõe **estigma, barreiras educacionais e profissionais**, além de sobrecarga familiar. Crianças enfrentam dificuldades de socialização e desempenho escolar; adultos, limitações no mercado de trabalho e maior risco de depressão e



ansiedade [5, 25, 77, 84]. **O tratamento precoce pode mitigar esses impactos, promovendo inclusão e autonomia.**

### **Vosoritida: Evidência Clínica e Segurança**

A vosoritida é um **análogo do CNP** que atua no **mecanismo molecular da doença**, antagonizando a via FGFR3 e restaurando o crescimento endocondral [116]. Ensaios clínicos de fase II e III demonstram:

- **Aumento significativo da VCA: +1,57 cm/ano** (5–18 anos, 111-301); até **+2,62 cm/ano** em <2 anos (111-208) vs. controle [40-42].
- **Melhora do escore Z de altura e proporcionalidade corporal** (p. ex., AS/AT e envergadura/altura), com **convergência em direção aos valores de referência** pediátricos e sem acelerar maturação óssea.
- **Segurança consistente**: eventos adversos leves, principalmente reações no local da injeção [116].
- **Extensões de longo prazo (até 7 anos)** confirmam **sustentabilidade do efeito** (+1.84 em meninos /1.44 em meninas cm/ano após 4 anos) e perfil de segurança estável [44-46].
- **Qualidade de vida**: ganhos significativos em QoLISSY e PedsQL, especialmente em domínios físico e social [21, 25, 44].

Dados de vida real, incluindo estudos brasileiros, reforçam esses achados, com benefícios equivalentes aos observados nos estudos pivotais. A vosoritida é aprovada pela **ANVISA (2021)** e por agências internacionais, já incorporada em países como **Alemanha, França, Austrália e Polônia**.

### **Avaliação Econômica no Contexto Brasileiro**

O modelo de **custo-utilidade** (perspectiva SUS, horizonte vitalício) mostra que a vosoritida gera **+6,3 QALYs** (18,7 vs. 12,4) em relação ao cuidado padrão, com custo incremental de **R\$ 7 milhões** e **RCEI de R\$ 1,0 milhão/QALY** [147]. Sem aplicação da taxa de desconto, o ganho seria **18,4 QALYs** e a RCEI cairia para **R\$ 508 mil/QALY**, evidenciando que a taxa de desconto subestima benefícios de terapias crônicas. Este resultado, apesar de estar em linha com outras tecnologias incorporadas para doenças raras incorporadas em anos recentes, reforça a **dificuldade de se esperar custo-**



**efetividade em cenários de introdução de tecnologias avançadas em áreas terapêuticas previamente desassistidas.**

O **impacto orçamentário** estimado é de **R\$ 2,4 bilhões em 5 anos** para 816 pacientes, com o desconto comercial proposto. Sem desconto comercial no preço, seria **R\$ 3,0 bilhões**, reforçando a importância da negociação. Este resultado deve ser interpretado no contexto de uma incorporação que permitirá **controle de critérios de inclusão e monitoramento**, além de evitar gastos desordenados e garantir equidade.

#### **Evidência Brasileira de Mundo Real e oportunidade de monitoramento: o Estudo 111-606**

Para robustecer a base de evidências nacionais, a BioMarin Brasil está conduzindo o estudo de mundo real **111-606** ("*Real-world effectiveness and safety of Voxzogo® in children with achondroplasia: An observational study in Brazil*"), um **estudo fase IV, observacional, multicêntrico e de coorte ambispectiva**, desenhado para avaliar a efetividade e a segurança da vosoritida na prática clínica de rotina no país. Os desfechos primários incluem altura/velocidade de crescimento anualizada (VCA) e escores Z, além de medidas de proporcionalidade corporal. O protocolo do estudo prevê duas análises interinas (primeira com dados até o final de 2025; segunda após o término do recrutamento) e análise final em meados de 2027. Até o dia 19 de agosto de 2025, 10 participantes estavam incluídos, com 6 centros elegíveis (2 ativos e 4 em fase final de ativação) e meta de 50 participantes. Informações mais detalhadas constam no Relatório de Progresso, no [ANEXO VII](#).

Esse investimento em geração de evidência local está alinhado ao fato de a vosoritida já ser reconhecida como padrão de tratamento etiológico da acondroplasia, reforçando a relevância clínica e a maturidade regulatória da tecnologia no manejo da doença no Brasil. Ademais, pelo desenho ambispectivo, pela infraestrutura de monitoramento e pela coleta estruturada de desfechos clínicos em condições de uso rotineiro, **o estudo 111-606 pode oferecer a base operacional para apoiar um eventual plano de monitoramento pós-incorporação no SUS, caso assim deliberado pela CONITEC, permitindo acompanhar a efetividade e a segurança no cenário de mundo real.**

#### ***Considerações Gerais***

A estimativa de custo apresentada no âmbito de processo de incorporação de medicamento no Sistema Único de Saúde ("SUS") é feita em um contexto que se avalia



dados amplos epidemiológicos da população brasileira, em que estabelece modelos específicos de disponibilização, centralização de entregas e tantos outros aspectos clínicos, comerciais, operacionais, financeiros e logísticos de um processo específico, robusto e complexo. Essa estimativa também leva em consideração o tamanho da população-alvo que será beneficiada pelo tratamento, elemento fundamental para que se alcance uma estimativa de preço custo-efetivo.

Dessa forma, é válido ressaltar que as condições de um fornecimento pontual de um produto a um indivíduo específico, em decorrência de uma ordem judicial, são absolutamente distintas das condições e do contexto das estimativas de custos de aquisição feitas no âmbito da incorporação de um produto no SUS. É dizer, as condições para atendimento de ordem judicial levam em consideração fornecimentos esporádicos e não previsíveis decorrentes da judicialização da saúde.

Ademais, também vale ressaltar que a proposta ofertada em uma venda pública, no caso de um pregão ou inexigibilidade de licitação, tem características específicas de volume, condições de entrega e pagamentos, estabelecidos no edital ou no pedido de orçamento e, portanto, particularidades diversas das condições analisadas no processo de submissão e incorporação de tecnologia perante a CONITEC.

Diferentemente das compras governamentais e por decisão judicial, as estimativas de custos indicadas à CONITEC levam em consideração fatores como fornecimento em maior escala e previsibilidade pelo período de cinco anos (artigo 47, inciso I, item 21, da Portaria nº 2.009/2012 do Ministério da Saúde).

Nas hipóteses de fornecimento de medicamentos em procedimentos de compra pública – realizada pelo Ministério da Saúde ou pelas Secretarias Estaduais de Saúde – ou de fornecimento para cumprimento de ordem judicial, o limite a ser praticado é o Preço Máximo de Venda ao Governo (“PMVG”),<sup>2</sup> devidamente majorado pela alíquota fiscal pertinente, em conformidade com as disposições da Resolução da Câmara de Regulação do Mercado de Medicamentos (“CMED”) nº 2/2004. O preço praticado em vendas públicas ou em fornecimentos decorrentes de judicialização da saúde, tampouco vinculam a companhia a eventuais condições futuras diversas de fornecimento.

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<sup>2</sup> “o **preço-teto** para vendas de medicamentos constantes do rol anexo ao (sic) Resolução CTE-CMED nº 6, de 27 de maio de 2021, ou **para atender ordem judicial**” e corresponde ao resultado da aplicação de um **desconto mínimo obrigatório** em relação ao Preço Fábrica (“PF”). Definição dada pela CMED e disponível em <https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos>.



No mais, a BioMarin registra que eventual tentativa de vincular a aplicação do preço de incorporação do VOXZOGO® (vosoritida) em condições e contextos diversos, como ocorre nas aquisições públicas ou fornecimento para atendimento judicial, violaria princípios como a segurança jurídica, a confiança legítima, e a boa-fé objetivas, todos consignados no julgamento do Tema nº 1234 pelo Supremo Tribunal Federal. Ademais, o Tema nº 1234 e a Súmula Vinculante nº 60 não obrigam a companhia a praticar um preço que não condiz com sua política comercial, e nem poderia ser assim, em atenção ao princípio da livre iniciativa, insculpido pelo artigo 170 da Constituição Federal, e regulamentado pela Lei de Declaração de Direitos de Liberdade Econômica (Lei 13.874/2019).

Por fim, a BioMarin ressalva que o preço estimado para a incorporação do VOXZOGO® (vosoritida) será observado somente após a completa incorporação do medicamento, isto é, mediante sua efetivação e disponibilização no SUS, nos termos preconizados pelo artigo 25, *caput*, do Decreto 7.646/2011.

### **Conclusão**

A acondroplasia é uma condição **grave, sistêmica e historicamente negligenciada**, com alta carga clínica, social e econômica. A vosoritida é a **única terapia etiológica aprovada**, com evidências robustas de eficácia, segurança e impacto positivo em qualidade de vida. O tratamento é aplicado pelos cuidadores dos pacientes em seu ambiente domiciliar, **sem sobrecarregar a infraestrutura de saúde** e facilitando a operacionalização da linha de cuidado. A efetividade da eventual incorporação poderá ser monitorada através do **estudo de mundo real já em andamento**. A elaboração do primeiro PCDT da acondroplasia, com a incorporação da vosoritida, será facilitada pela **existência de consensos de tratamento bem reconhecidos e de uma diretriz desenvolvida pela Sociedade Brasileira de Pediatria, que preconizam e orientam o monitoramento antropométrico padronizado**.

A incorporação da vosoritida ao SUS é **tecnicamente justificada, socialmente necessária e economicamente viável**, com o potencial de reduzir a **carga de complicações e ampliar a independência funcional** das novas gerações de cidadãos com acondroplasia no Brasil, representando um passo decisivo para **equidade, inclusão e benefício social** no Brasil.



## Requerimentos para Garantia da Legalidade, Motivação e Transparência do Processo

À luz do art. 37 da Constituição da República, que consagra os princípios da legalidade, publicidade, motivação e eficiência na Administração Pública, bem como do disposto na Lei nº 8.080/1990 (art. 6º e art. 19-Q) e na Lei nº 12.401/2011, que regulamentam a atuação da Conitec, requer-se que o processo de análise e decisão sobre a presente demanda de incorporação observe os seguintes parâmetros mínimos:

### 1. Estudos de Custo-Efetividade

Apresentação dos fundamentos de análise do custo-efetividade detalhado, sob a perspectiva do Sistema Único de Saúde (SUS), com descrição da metodologia empregada, fontes utilizadas, premissas adotadas, horizonte temporal, taxa de desconto, alternativas comparativas já incorporadas e cálculo do ICER (*Incremental Cost-Effectiveness Ratio*) e utilidade (QALY/AVG) ou outra razão incremental validada.

Caso algum desses elementos metodológicos não seja utilizado, requer-se motivação expressa, sob pena de nulidade por vício de motivação.

### 2. Estimativa de Impacto Orçamentário

Elaboração de estudo de impacto orçamentário transparente, contendo: metodologia, premissas e parâmetros epidemiológicos (prevalência e incidência), cenários possíveis (alternativos) de adesão, variação de preços e custos diretos e indiretos envolvidos, considerando-se horizonte temporal razoável.

Atendendo ao princípio da razoabilidade e ao dever de motivação, a decisão deverá explicitar, mediante **fundamentação lógica e adequada (razoável)**, de que modo os **dados e parâmetros** apresentados foram considerados, bem como justificar eventuais exclusões ou descon siderações, sob pena de nulidade por vício de motivação.

### 3. Delimitação da Perspectiva do SUS

Que a Conitec esclareça expressamente o que considera como “Sistema Único de Saúde” para fins de análise econômica, especificando se estão incluídos custos relativos à atenção à saúde individual e coletiva, assistência terapêutica integral e farmacêutica, formação de profissionais de saúde, atenção básica e comunitária, vigilância em saúde, promoção da saúde, formação e capacitação de recursos



humanos, pesquisas e desenvolvimento, gestão e participação social, conforme previsto no art. 6º da Lei nº 8.080/1990.

Que explicita, ainda, os **custos já suportados pelo SUS em razão do tratamento** (ou do tratamento insuficiente) da doença em questão, considerando que não há alternativa terapêutica equivalente.

A omissão ou simplificação dessa análise compromete a motivação da decisão e desconsidera a abrangência legal da atuação do SUS.

#### **4. Motivação da Decisão**

A decisão final deverá conter fundamentação clara, suficiente e individualizada, indicando as razões de fato (notadamente, as evidências técnicas) e de direito que conduziram ao acolhimento ou rejeição da incorporação.

É imprescindível que a Conitec responda de forma explícita aos argumentos e evidências apresentados pelo demandante e pelos demais participantes, sob pena de vício de motivação.

Alinhada com documentação e requerimentos apresentados, a BioMarin reafirma seu compromisso em trabalhar de forma conjunta para viabilizar a incorporação do medicamento e superar eventuais obstáculos — sejam eles clínicos, econômicos ou de outra natureza.

#### **5. Publicidade e Transparência**

Requer-se a divulgação integral dos pareceres técnicos, estudos econômicos, atas e relatórios produzidos durante a tramitação, garantindo o acesso público às informações que embasaram a decisão.

A publicidade é condição de validade do ato administrativo, nos termos do art. 37 da Constituição e da Lei nº 12.527/2011 (Lei de Acesso à Informação).

#### **6. Participação e Contraditório Administrativo**

Solicita-se que seja assegurado ao demandante, bem como a entidades da sociedade civil e especialistas da área, o direito de participação efetiva em eventuais audiências ou consultas públicas ou reuniões deliberativas.

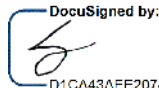


A ausência de oportunidade de manifestação e respectivas respostas motivadas caracteriza cerceamento de participação e vício de legalidade.

## **7. Isonomia e Precedentes Administrativos**

Havendo medicamentos ou tecnologias de perfil semelhante já incorporados, requer-se que a decisão explicita, de forma motivada, as distinções técnicas e econômicas que justificam eventual tratamento diferenciado.

Assim, requer-se que eventual decisão divergente explicita, de forma motivada, as distinções técnicas e econômicas que justificam tratamento diverso. A omissão nesse ponto importará em violação ao princípio da isonomia.

DocuSigned by:  


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**BioMarin Brasil Farmacêutica Ltda.**

Patrice Yvon Gracian Lebrun

Representante Legal

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## **9. ANEXOS**

### **9.1. ANEXO I – Bula do produto**

**Voxzogo<sup>®</sup>**  
vosoritida

## APRESENTAÇÕES

**Voxzogo 0,4 mg:** embalagem com 10 frascos-ampola de pó liofilizado para solução injetável contendo 0,4 mg de vosoritida, 10 seringas preenchidas com 0,5 mL de diluente, 10 agulhas para transferência do diluente e 10 seringas para aplicação.

**Voxzogo 0,56 mg:** embalagem com 10 frascos-ampola de pó liofilizado para solução injetável contendo 0,56 mg de vosoritida, 10 seringas preenchidas com 0,7 mL de diluente, 10 agulhas para transferência do diluente e 10 seringas para aplicação.

**Voxzogo 1,2 mg:** embalagem com 10 frascos-ampola de pó liofilizado para solução injetável contendo 1,2 mg de vosoritida, 10 seringas preenchidas com 0,6 mL de diluente, 10 agulhas para transferência do diluente e 10 seringas para aplicação.

Cada frasco-ampola e seringa preenchida com diluente deve ser apenas para uso único.

## USO SUBCUTÂNEO

### USO ADULTO E PEDIÁTRICO ACIMA DE 6 MESES

## COMPOSIÇÃO

### **Voxzogo 0,4 mg**

Cada frasco-ampola de **Voxzogo** contém 0,4 mg de vosoritida.

Após reconstituição, cada frasco-ampola contém 0,4 mg de vosoritida em 0,5 mL de solução, correspondendo a uma concentração de 0,8 mg/mL.

### **Voxzogo 0,56 mg**

Cada frasco-ampola de **Voxzogo** contém 0,56 mg de vosoritida.

Após reconstituição, cada frasco-ampola contém 0,56 mg de vosoritida em 0,7 mL de solução, correspondendo a uma concentração de 0,8 mg/mL.

### **Voxzogo 1,2 mg**

Cada frasco-ampola de **Voxzogo** contém 1,2 mg de vosoritida.

Após reconstituição, cada frasco-ampola contém 1,2 mg de vosoritida em 0,6 mL de solução, correspondendo a uma concentração de 2 mg/mL.

Excipientes: ácido cítrico mono-hidratado, citrato de sódio di-hidratado, trealose di-hidratada, manitol, metionina, polissorbato 80.

**Diluyente:** água para injetáveis.

## INFORMAÇÕES TÉCNICAS AOS PROFISSIONAIS DE SAÚDE

### 1. INDICAÇÕES

**Voxzogo** é indicado para o tratamento da acondroplasia em pacientes pediátricos a partir de 6 meses de idade cujas e epífises não estão fechadas. O diagnóstico de acondroplasia deve ser confirmado por teste genético apropriado.

### 2. RESULTADOS DE EFICÁCIA

A eficácia e a segurança de vosoritida em pacientes com acondroplasia com mutação FGFR3 confirmada foram avaliadas em um estudo de 52 semanas randomizado, duplo-cego, controlado por placebo (estudo ACH 111-301). No estudo ACH 111-301, os pacientes foram randomizados para vosoritida (n = 60) ou placebo (n = 61) e a dose de vosoritida foi de 15 mcg/kg, administrada por via subcutânea uma vez ao dia. Antes da randomização, todos os pacientes foram incluídos em um estudo observacional (estudo ACH 111-901) para pacientes pediátricos com acondroplasia por pelo menos um período de 6 meses durante o qual a altura inicial de pé e outras avaliações de crescimento pré-tratamento foram coletadas. Pacientes com cirurgia de alongamento de membro nos 18 meses anteriores ou que planejavam fazer a cirurgia de alongamento de membro durante o período do estudo, foram excluídos. O estudo compreendeu uma fase de tratamento controlada por placebo de 52 semanas seguida por um estudo aberto de extensão no qual todos os pacientes receberam vosoritida. O desfecho primário de eficácia foi a alteração na velocidade de crescimento anual (VCA) a partir da linha de base até a Semana 52 em comparação com o grupo placebo.

Os pacientes com acondroplasia também foram tratados com 15 mcg/kg/dia de **Voxzogo** em um estudo aberto de escalonamento de dose e em seu estudo de extensão de longo prazo (estudo ACH 111-205). Os dados de pacientes foram coletados de estudos observacionais para caracterizar a história natural da acondroplasia. Os dados de altura dos pacientes com acondroplasia não tratados

da mesma faixa etária que os pacientes dos estudos clínicos foram usados como um controle histórico para avaliar o efeito na altura após um período de até 5 anos de tratamento com **Voxzogo**.

Os dados demográficos dos pacientes e as características basais são mostrados na Tabela 1.

Tabela 1: Dados demográficos e características dos pacientes no estudo ACH 111-301 e no estudo ACH 111-205

Parâmetro	Estudo ACH 111-301		Estudo ACH 111-205 <sup>b</sup>
	Placebo (n=61)	<b>Voxzogo</b> 15 mcg/kg/dia (n=60)	<b>Voxzogo</b> 15 mcg/kg/dia (n=10)
Idade no Dia 1 (anos)			
Média (DP)	9,06 (2,47)	8,35 (2,43)	8,54 (1,54)
Mín, Máx	5,1; 14,9	5,1; 13,1	6,3; 11,1
Idade no Dia 1, n (%) <sup>a</sup>			
≥5 a <8 anos	24 (39,3)	31 (51,7)	4 (40,0)
≥8 a <11 anos	24 (39,3)	17 (28,3)	5 (50,0)
≥11 a <15 anos	13 (21,3)	12 (20,0)	1 (10,0)
Estágio de Tanner, n (%) <sup>a</sup>			
I	48 (78,7)	48 (80,0)	10 (100,0)
>I	13 (21,3)	12 (20,0)	
Sexo, n (%) <sup>a</sup>			
Masculino	33 (54,1)	31 (51,7)	4 (40,0)
Feminino	28 (45,9)	29 (48,3)	6 (60,0)
Peso (kg)			
Média (DP)	24,62 (9,07)	22,88 (7,96)	25,13 (5,74)
Mín, Máx	11,6; 68,9	13,6; 53,0	18,2; 36,4

Máx: máximo; Mín: mínimo; DP: desvio padrão.

<sup>a</sup> As porcentagens foram calculadas usando o número total de pacientes no conjunto de análise completo (N para cada grupo de tratamento) como denominador.

<sup>b</sup> Análise de 10 dos 35 pacientes que receberam apenas 15 mcg/kg/dia em um estudo aberto de escalonamento de dose e que continuaram no estudo de extensão de longa duração ACH 111-205.

No estudo ACH 111-301, foram observadas melhoras na VCA e no escore Z da altura em relação ao valor basal em pacientes tratados com 15 mcg/kg/dia de **Voxzogo** em comparação com o grupo placebo. Os resultados de eficácia são mostrados na Tabela 2.

Tabela 2: Resultados do estudo clínico controlado por placebo

	Placebo (n=61)			15 mcg/kg de Voxzogo diariamente (n=60 <sup>c</sup> )			Voxzogo vs. Placebo
	Valor basal	Semana 52	Alteração	Valor basal	Semana 52	Alteração	Diferença média do MQ nas alterações (IC 95%)
<b>Velocidade de crescimento anualizada (cm/ano)</b>							
Média ± DP	4,06 ± 1,20	3,94 ± 1,07	-0,12 ± 1,74	4,26 ± 1,53	5,61 ± 1,05	1,35 ± 1,71	<b>1,57<sup>a</sup></b> <b>(1,22; 1,93)</b> <b>(p = &lt;0,0001)<sup>b</sup></b>
<b>Escore Z de altura</b>							
Média ± DP	-5,14 ± 1,07	-5,14 ± 1,09	0,00 ± 0,28	-5,13 ± 1,11	-4,89 ± 1,09	0,24 ± 0,32	<b>0,28<sup>a</sup></b> <b>(0,17; 0,39)</b> <b>(p = &lt;0,0001)<sup>b</sup></b>

VCA: velocidade de crescimento anualizada; IC 95%: intervalo de confiança de 95%; MQ: mínimo quadrado; DP: desvio padrão.

<sup>a</sup> A diferença é 15 mcg/kg de **Voxzogo** menos placebo.

<sup>b</sup> Valor p bilateral.

<sup>c</sup> Dois pacientes do grupo **Voxzogo** saíram do estudo antes da Semana 52. Os valores para esses 2 pacientes foram imputados para esta análise.

Média de MQ estimada a partir do modelo ANCOVA (análise de covariância) ajustado para diferenças de valor basal entre os dois braços, análise de covariância.

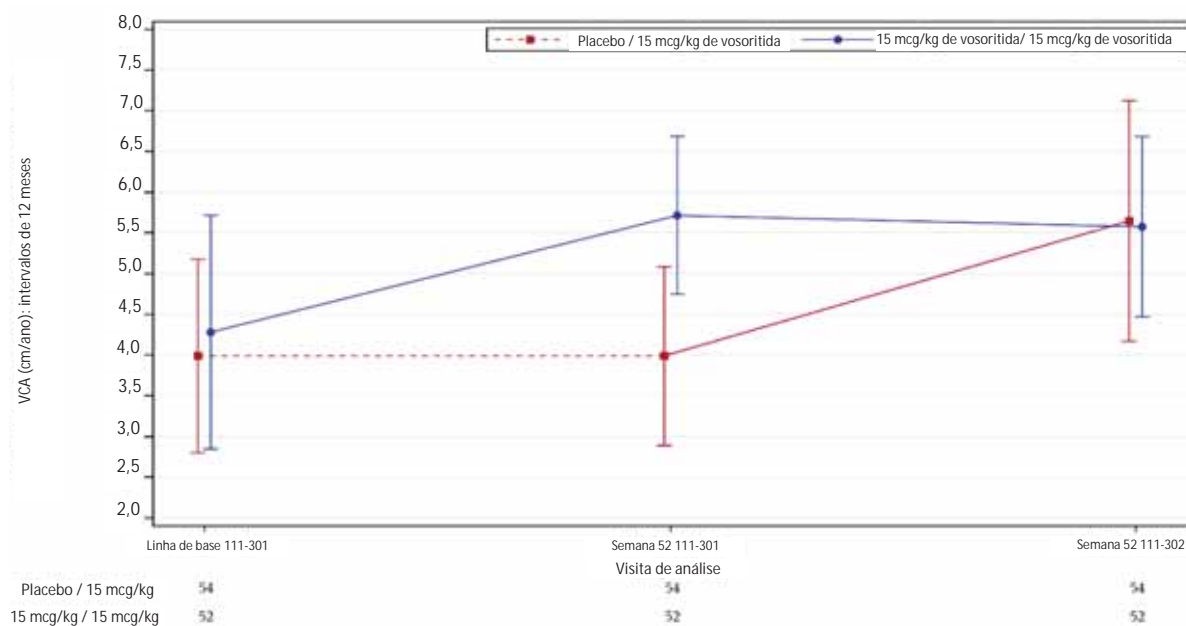
O benefício da melhora na VCA em favor de **Voxzogo** foi consistente em todos os subgrupos predefinidos analisados, incluindo sexo, faixa etária, estágio de Tanner, escore Z na linha de base e VCA na linha de base. No subgrupo do sexo masculino no estágio de Tanner >I, a estimativa pontual do efeito do tratamento foi em favor de vosoritida, no entanto, havia apenas 8 indivíduos neste subgrupo (3 e 5 indivíduos nos braços que receberam vosoritida e placebo, respectivamente).

O aumento de crescimento observado ocorreu proporcionalmente tanto na coluna quanto nos membros inferiores. Não houve diferença na densidade mineral óssea após o tratamento com **Voxzogo** em comparação com o placebo. Durante o tratamento com esse medicamento, o aumento médio da idade óssea foi comparável ao aumento médio da idade cronológica, indicando que não houve aceleração da maturação óssea.

A Figura 1 mostra o efeito de **Voxzogo** durante o período de dois anos no grupo de tratamento com **Voxzogo**, bem como o efeito no grupo de controle com placebo após receber injeções subcutâneas

diárias de **Voxzogo** por 52 semanas no estudo aberto de extensão. As melhorias na VCA mantiveram-se durante a continuação do tratamento com **Voxzogo**, sem evidências de taquifilaxia.

Figura 1: Média ( $\pm$ DP) do intervalo de 12 meses da VCA ao longo do tempo



A Figura 1 inclui todos os indivíduos incluídos no estudo pivotal que tiveram uma avaliação de altura na Semana 52 no estudo de extensão. As linhas sólidas representam o tratamento com 15 mcg/kg de vosoritida; as linhas tracejadas representam o placebo. A linha de base é definida como a última avaliação antes da primeira dose do princípio ativo do estudo (ou seja, vosoritida) ou placebo no estudo 111-301.

A VCA em 12 meses nas visitas pós-linha de base é derivada dos 12 meses anteriores. Por exemplo, intervalo de 12 meses de VCA na Semana 52 do 111-302 = [(altura na visita da Semana 52 no 111-302 - altura na visita da Semana 52 no 111-301)/(data da visita da Semana 52 no 111-302 - data da visita da Semana 52 no 111-301)] x 365,25.

### Estudo aberto de extensão

No estudo de extensão de longo prazo (estudo ACH 111-205), 10 pacientes foram tratados com uma dose de 15 mcg/kg/dia de **Voxzogo** continuamente por 5 anos. A melhora média (DP) da VCA em comparação com o valor basal aos 60 meses foi de 1,34 (1,31) cm/ano.

O ganho de altura após 5 anos de tratamento com 15 mcg/kg/dia de **Voxzogo** foi comparado com um controle histórico pareado por idade e sexo. A análise comparativa transversal de 5 anos

ajustada para diferenças de altura do valor basal demonstrou que houve uma diferença média estatisticamente significativa (IC 95%) na altura em favor do grupo tratado com **Voxzogo** [9,08 (5,77; 12,38) cm;  $p = 0,0002$ ] em comparação com pacientes com acondroplasia não tratados.

### **População pediátrica < 5 anos**

Um total de 75 pacientes com idades entre 4,4 e 59,8 meses no Dia 1 da dosagem foram inscritos em um estudo randomizado, duplo cego e controlado por placebo com duração de 52 semanas. Pelo menos 6 meses de dados basais de crescimento foram coletados no estudo observacional para pacientes com idade igual ou superior a 6 meses no momento da randomização, e pelo menos 3 meses de dados basais para os indivíduos com idade inferior a 6 meses no momento da randomização. Um total de 64 pacientes foram randomizados para receber tratamento no estudo com vosoritida ou placebo e 11 pacientes receberam tratamento no estudo aberto. Durante 52 semanas, os pacientes tratados com vosoritida tiveram uma melhora no escore Z de altura de +0,30 DP (IC 95% 0,07; 0,54) em comparação com o placebo. Foi observado um efeito consistente a favor de **Voxzogo** em todos os pacientes a partir de 6 meses de idade.

Nove crianças com idades acima de 24 e abaixo de 60 meses foram tratadas com vosoritida por 3 anos e mostraram uma melhora no escore Z de altura de +1,22 DP (IC 95% 0,78; 1,66) e uma diferença média dos MQ na altura de 5,73 cm (IC 95% 3,54; 7,93) em comparação com um controle histórico pareado por idade e sexo de pacientes com acondroplasia não tratados.

Onze crianças com idades acima de 6 e abaixo de 24 meses foram tratadas com vosoritida por 2 anos e mostraram uma melhora no escore Z de altura de 0,79 DP (IC 95% 0,29; 1,28) e uma diferença média de MQ na altura de 2,69 cm (IC 95% 1,00; 4,38) em comparação com um controle histórico pareado por idade e sexo de pacientes com acondroplasia não tratados.

Os perfis de segurança e eficácia foram semelhantes em crianças a partir de 6 meses e menores de 5 anos de idade em comparação com crianças com 5 anos ou mais.

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### 3. CARACTERÍSTICAS FARMACOLÓGICAS

#### Mecanismo de ação

Vosoritida é um peptídeo natriurético modificado tipo C (CNP). Em pacientes com acondroplasia, o crescimento endocondral do osso é regulado negativamente devido a uma mutação do tipo ganho de função do receptor 3 do fator de crescimento de fibroblastos (FGFR3). A ligação de vosoritida ao receptor de peptídeo natriurético tipo B (NPR-B) antagoniza a sinalização a jusante (*downstream*) do FGFR3 ao inibir as quinases extracelulares 1 e 2 reguladas por sinal (ERK1/2) na via da proteína quinase ativada por mitogênese (MAPK) no nível do fibrossarcoma rapidamente acelerado serina/treonina proteína quinase (RAF-1). Como resultado, vosoritida, como o peptídeo natriurético tipo C (CNP), atua como um regulador positivo do crescimento endocondral do osso, pois promove a proliferação e diferenciação dos condrócitos.

#### Propriedades farmacodinâmicas

Aumentos dependentes da exposição (AUC e  $C_{máx}$ ) da linha de base em concentrações urinárias de guanosina monofosfato cíclico (cGMP, um biomarcador para a atividade do NPR-B), bem como do marcador de colágeno e soro tipo X (CXM, um biomarcador de formação óssea endocondral), foram observados durante o tratamento com vosoritida. O aumento nas concentrações urinárias de cGMP a partir da linha de base pré-dose ocorreu nas primeiras quatro horas após a dose. A concentração sérica média de CXM aumentou em relação ao valor da linha de base no Dia 29 da administração diária deste medicamento. Esse efeito foi mantido além de 24 meses de tratamento.

A atividade de vosoritida medida por cGMP na urina estava próxima da saturação, enquanto o aumento máximo na atividade da placa de crescimento indicada por CXM foi alcançado na dose de 15 mcg/kg administrada por via subcutânea uma vez ao dia.

#### Propriedades farmacocinéticas

Vosoritida é um CNP humano recombinante modificado, produzido a partir de *Escherichia coli* usando tecnologia de DNA recombinante. O análogo de peptídeo de 39 aminoácidos inclui os 37 aminoácidos C terminais da sequência do CNP53 humano mais a adição de 2 aminoácidos (Pro e

Gly) para transmitir resistência à degradação pela endopeptidase neutra (NEP), resultando em meia-vida prolongada em comparação com o CNP endógeno.

A farmacocinética de vosoritida foi avaliada em um total de 58 pacientes de 5 a 18 anos com acondroplasia, que receberam injeções subcutâneas de vosoritida em doses de 15 mcg/kg uma vez ao dia durante 52 semanas.

### **Absorção**

Vosoritida foi absorvido com um  $T_{máx}$  mediano de 15 minutos. A concentração média ( $\pm$  DP) de pico ( $C_{máx}$ ) e a área sob a curva de concentração-tempo a partir do tempo zero até a última concentração mensurável ( $AUC_{0-t}$ ), observada após 52 semanas de tratamento, foi 5.800 ( $\pm$  3.680) e 290.000 ( $\pm$  235.000) pg-min/mL, respectivamente. A biodisponibilidade de vosoritida não foi avaliada em estudos clínicos.

### **Distribuição**

O volume médio ( $\pm$  DP) de distribuição aparente após 52 semanas de tratamento foi de 2.910 ( $\pm$  1.600) mL/kg.

### **Metabolismo**

Espera-se que o metabolismo de vosoritida ocorra por vias catabólicas e seja degradado em pequenos fragmentos de peptídeos e aminoácidos.

### **Eliminação**

A depuração média aparente ( $\pm$  DP) após 52 semanas de tratamento foi 79,4 (53,0) mL/min/kg. A meia-vida média ( $\pm$  DP) foi 27,9 (9,9) minutos.

A variabilidade (coeficiente de variação) interindivíduos na depuração aparente foi de 33,6%.

### **Linearidade/não linearidade**

O aumento da exposição plasmática ( $AUC$  e  $C_{máx}$ ) com a dose foi maior do que proporcional à dose no intervalo de dose de 2,5 (0,17 vezes a dose recomendada) a 30,0 mcg/kg/dia (duas vezes a dose aprovada).

### **Populações especiais**

Não foram observadas diferenças clinicamente significativas na farmacocinética de vosoritida com base em idade (0,9 a 16 anos), sexo, raça ou etnia.

### **População pediátrica abaixo de 5 anos**

As exposições farmacocinéticas em crianças a partir de 6 meses e menores de 5 anos de idade foram consistentes com a população pediátrica mais velha estudada de acordo com a dose recomendada.

### **Peso corporal**

O peso corporal é a única covariável significativa para a depuração ou o volume de distribuição de vosoritida. A depuração aparente e o volume de distribuição de vosoritida aumentaram com o aumento do peso corporal em pacientes com acondroplasia (9 a 74,5 kg). A posologia proposta leva em consideração esse desvio e recomenda o uso de doses acima (em pacientes entre 10 e 16 kg de peso corporal) ou abaixo (naqueles acima de um peso corporal de 44 kg) da "dose padrão" de 15 mcg/kg a fim de permitir um nível semelhante de exposição em todas as faixas de peso.

### **Pacientes com comprometimento renal e hepático**

A segurança e a eficácia de vosoritida em pacientes com comprometimento renal ou hepático não foram avaliadas. Com base no mecanismo de eliminação, não é esperado que o comprometimento renal ou hepático altere a farmacocinética de vosoritida.

### **Estudos de interação medicamentosa**

Estudos de inibição e indução do citocromo P450 (CYP) *in vitro* indicaram que vosoritida não inibiu CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 ou 3A4/5, nem induziu CYP 1A2, 2B6 ou 3A4/5 em concentrações clinicamente relevantes. Estudos de interação *in vitro* também indicaram que o potencial de interação com os transportadores de fármacos OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, KATE2-K, BCRP, P-gp e BSEP é baixo em concentrações clinicamente relevantes.

### **Dados pré-clínicos de segurança**

Reações adversas não foram observadas em estudos clínicos, mas foram observadas em animais com níveis de exposição semelhantes aos níveis de exposição clínica e com possível relevância para o uso clínico.

Diminuições transitórias da pressão arterial e aumentos da frequência cardíaca foram observados em macacos saudáveis em vários estudos em doses de 28 a 300 mcg/kg de maneira relacionada à dose. Os efeitos máximos foram tipicamente observados na primeira hora após a administração da dose e foram geralmente assintomáticos. Em alguns macacos recebendo doses elevadas de

vosoritida, breves episódios de decúbito esternal/lateral ou hipoatividade foram observados. Esses efeitos podem estar relacionados à diminuição na pressão arterial.

Efeitos adversos na postura corporal, forma óssea, mobilidade e resistência óssea foram observados em animais normais em estudos de toxicidade de dose repetida em ratos e macacos. Em macacos, o nível de efeito adverso não observado (NOAEL) para vosoritida é de 25 mcg/kg (valor médio de  $C_{máx}$  de 1.170 pg/mL; aproximadamente equivalente à dose humana recomendada em um ser humano de 20 kg) quando administrado diariamente por injeção subcutânea durante 44 semanas.

### **Carcinogenicidade e mutagênese**

Não foram realizados estudos de carcinogenicidade e genotoxicidade com vosoritida. Com base no mecanismo de ação, não se espera que vosoritida seja tumorigênico.

### **Comprometimento da fertilidade**

Em um estudo de fertilidade e reprodução ratos machos e fêmeas com níveis de dose de até 540 mcg/kg/dia, vosoritida não teve efeito no desempenho de acasalamento, fertilidade ou nas características da ninhada.

### **Toxicidade reprodutiva e de desenvolvimento**

Vosoritida não foi associado a efeitos no desempenho reprodutivo, *in utero* ou parâmetros de desenvolvimento medidos em ratos e coelhos para investigar a fertilidade ou o desenvolvimento embriofetal em estudos de desenvolvimento pré e pós-natal.

Vosoritida foi detectado no leite materno em ratos.

## **4. CONTRAINDICAÇÕES**

Hipersensibilidade ao princípio ativo ou a qualquer um dos excipientes da formulação.

## **5. ADVERTÊNCIAS E PRECAUÇÕES**

### **Efeitos sobre a pressão arterial**

Pacientes com doenças cardíacas ou vasculares significativas e pacientes em tratamento com medicamentos anti-hipertensivos foram excluídos dos estudos clínicos.

Para mitigar o risco de uma possível redução da pressão arterial e sintomas associados (tontura, fadiga e/ou náusea), os pacientes devem estar bem hidratados no momento da injeção (vide itens “Posologia e Modo de Usar” e “Reações Adversas”).

### **Sódio**

**Voxzogo** contém menos de 1 mmol de sódio (23 mg) por unidade de volume, ou seja, é praticamente “livre de sódio”.

### **Gravidez**

Não há dados ou os dados existentes são limitados sobre o uso de vosoritida em gestantes. Os estudos em animais não indicam efeitos nocivos diretos ou indiretos no que diz respeito à toxicidade reprodutiva (vide item “Características Farmacológicas”). Como medida de precaução, é preferível evitar o uso de **Voxzogo** durante a gravidez.

**Categoria B: Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista.**

### **Lactação**

Os dados farmacodinâmicos/toxicológicos disponíveis em animais mostraram excreção de vosoritida no leite (vide item “Características Farmacológicas”).

O risco para recém-nascidos/lactentes não pode ser excluído. Vosoritida não deve ser utilizado durante a amamentação.

### **Fertilidade**

Não foi observado comprometimento da fertilidade masculina ou feminina em estudos pré-clínicos.

### **Uso pediátrico**

Os perfis de segurança e eficácia de **Voxzogo** em estudos clínicos envolvendo crianças a partir de 6 meses e menores de 5 anos de idade foram semelhantes ao observado em crianças mais velhas.

### **Efeito sobre a capacidade de dirigir veículos e operar máquinas**

**Voxzogo** tem influência moderada na capacidade de dirigir veículos, andar de bicicleta e utilizar máquinas. Vosoritida pode causar diminuições transitórias da pressão arterial, que são geralmente leves, porém, síncope, pré-síncope e tonturas, bem como outros sinais e sintomas de diminuição da pressão arterial, foram reportados como reações adversas com **Voxzogo**. A resposta do paciente

ao tratamento deve ser considerada e, se apropriado, o paciente deve ser aconselhado a não dirigir, andar de bicicleta ou usar máquinas por pelo menos 60 minutos após a injeção.

## 6. INTERAÇÕES MEDICAMENTOSAS

Foram realizados estudos de inibição e indução do citocromo P450 (CYP) *in vitro* e estudos de inibição do transportador *in vitro*. Os resultados sugeriram que é improvável que vosoritida cause interações medicamentosas mediadas por CYP ou por transportador em humanos quando vosoritida é administrado concomitantemente a outros medicamentos.

Não foram realizados outros estudos de interação. Por ser uma proteína humana recombinante, vosoritida é um candidato improvável para interações medicamentosas.

## 7. CUIDADOS DE ARMAZENAMENTO DO MEDICAMENTO

Armazenar em geladeira (de 2°C a 8°C). Não congelar. Proteger da luz.

**Voxzogo** pode ser armazenado em temperatura ambiente (de 15°C a 30°C) por um período único de até 90 dias, mas não além da data de validade. Não retornar **Voxzogo** ao refrigerador após o armazenamento em temperatura ambiente.

Os frascos-ampola fechados são válidos por 36 meses a partir da data de fabricação, impressa na embalagem do medicamento.

A estabilidade química e física da solução reconstituída suporta o armazenamento da solução por 3 horas em temperatura ambiente (de 15°C a 30°C).

Do ponto de vista microbiológico, a menos que o método de reconstituição exclua o risco de contaminação microbiana, a solução deve ser usada imediatamente.

**Se não for utilizada imediatamente, a solução reconstituída de Voxzogo deve ser administrada dentro de 3 horas após a reconstituição.**

**Antes de usar, observe o aspecto do medicamento.**

**Voxzogo** é fornecido como um pó liofilizado branco a amarelo e o diluente é uma solução límpida e incolor. Após dissolver o pó liofilizado no diluente, a solução gerada é um líquido límpido, incolor a amarelo.

**Número de lote e datas de fabricação e validade: vide embalagem.**

**Não use medicamento com o prazo de validade vencido. Guarde-o em sua embalagem original.**

**Todo medicamento deve ser mantido fora do alcance das crianças.**

## **8. POSOLOGIA E MODO DE USAR**

**Voxzogo** é administrado como uma injeção subcutânea diária. A dose recomendada baseia-se no peso do paciente, que varia entre 15-30 mcg/kg, em que a dose mais elevada é administrada às crianças menores (vide Tabela 3).

A dose pode ser administrada utilizando seringas graduadas em mililitros (mL) ou seringas graduadas em Unidades (U) (vide Tabela 3). As medições nas seringas graduadas em Unidades são equivalentes às das seringas graduadas em mL, de acordo com a seguinte fórmula: 0,1 mL = 10 Unidades. Por razões de praticidade e para levar em consideração alterações farmacocinéticas relacionadas ao peso (vide item “Propriedades farmacocinéticas”), a dosagem a seguir é recomendada.

Tabela 3: Volumes de dose única por peso corporal em volumes em mililitros (mL) e em Unidades (U)

Peso corporal (kg)	Dose (mg)	Voxzogo 0,4 mg		Voxzogo 0,56 mg		Voxzogo 1,2 mg	
		Diluyente (água para injetáveis): 0,5 mL		Diluyente (água para injetáveis): 0,7 mL		Diluyente (água para injetáveis): 0,6 mL	
		Concentração: 0,8 mg/mL		Concentração: 0,8 mg/mL		Concentração: 2 mg/mL	
		Volume de injeção diária					
		mL	Unidades	mL	Unidades	mL	Unidades
<b>5</b>	0,16 mg	0,20 mL	20 U				
<b>6-7</b>	0,20 mg	0,25 mL	25 U				
<b>8-11</b>	0,24 mg	0,30 mL	30 U				

Peso corporal (kg)	Dose (mg)	Voxzogo 0,4 mg		Voxzogo 0,56 mg		Voxzogo 1,2 mg	
		Diluyente (água para injetáveis): 0,5 mL		Diluyente (água para injetáveis): 0,7 mL		Diluyente (água para injetáveis): 0,6 mL	
		Concentração: 0,8 mg/mL		Concentração: 0,8 mg/mL		Concentração: 2 mg/mL	
		Volume de injeção diária					
		mL	Unidades	mL	Unidades	mL	Unidades
<b>12-16</b>	0,28 mg			0,35 mL	35 U		
<b>17-21</b>	0,32 mg			0,40 mL	40 U		
<b>22-32</b>	0,40 mg			0,50 mL	50 U		
<b>33-43</b>	0,50 mg					0,25 mL	25 U
<b>44-59</b>	0,60 mg					0,30 mL	30 U
<b>60-89</b>	0,70 mg					0,35 mL	35 U
<b>≥ 90</b>	0,80 mg					0,40 mL	40 U

### Duração do tratamento

O tratamento com este medicamento deve ser interrompido após a confirmação de que não existe potencial de crescimento adicional, indicado por uma velocidade de crescimento <1,5 cm/ano e fechamento das epífises.

### Doses esquecidas

Se uma dose de **Voxzogo** for esquecida, ela pode ser administrada em até 12 horas. Se mais de 12 horas tiverem passado desde o esquema posológico original, a dose esquecida NÃO deve ser administrada.

Oriente os pacientes/cuidadores a continuarem com a próxima dose programada no dia seguinte.

### Monitoramento de crescimento

Os pacientes devem ser monitorados e avaliados regularmente a cada 3-6 meses para verificar o peso corporal, o crescimento e o desenvolvimento físico. A dose deve ser ajustada de acordo com o peso corporal do paciente (vide Tabela 3).

### **Pacientes com comprometimento renal ou hepático**

A segurança e a eficácia de vosoritida em pacientes com comprometimento renal ou hepático não foram avaliadas.

**Instruções de uso:** **Voxzogo** destina-se apenas a administração subcutânea única. Este medicamento deve ser administrado em até 3 horas após a reconstituição.

Antes da administração, o profissional de saúde deve:

- treinar os cuidadores sobre a preparação e a injeção subcutânea deste medicamento.
- treinar os cuidadores e pacientes para reconhecer sinais e sintomas de diminuição da pressão arterial.
- informar os cuidadores e pacientes sobre o que fazer em caso de diminuição sintomática da pressão arterial.

Os pacientes e cuidadores devem ser instruídos a alternar os locais das injeções subcutâneas. Os locais de injeção recomendados incluem a parte anterior média das coxas, a parte inferior do abdômen, exceto 5 cm diretamente ao redor do umbigo, a parte superior das nádegas ou a parte de trás dos braços. A mesma área de injeção não deve ser usada em dois dias consecutivos. **Voxzogo** não deve ser injetado em locais que estejam vermelhos, inchados ou sensíveis.

Os pacientes devem estar bem hidratados no momento da injeção. É recomendado que os pacientes comam um lanche leve e bebam uma quantidade adequada de líquido (por exemplo, água, leite, suco etc.) cerca de 30 minutos antes da injeção. Isso serve para reduzir os sinais e sintomas de possíveis diminuições da pressão arterial (tonturas, fadiga e/ou náuseas) que podem ocorrer (vide “Efeitos sobre a pressão arterial” do item “Advertências e Precauções”).

Se possível, esse medicamento deve ser injetado aproximadamente à mesma hora todos os dias.

Após a reconstituição, **Voxzogo** é um líquido claro, incolor a amarelo. A solução não deve ser usada se estiver descolorida ou turva, ou se houver partículas.

**Reconstituição e administração:** Preparação de **Voxzogo** para injeção subcutânea:

- A embalagem contendo a correta concentração de **Voxzogo** e a correta seringa preenchida com diluente (volume de reconstituição) devem ser confirmadas com base no peso corporal do paciente (vide Tabela 3).
- Todos os suprimentos auxiliares necessários devem estar disponíveis antes de iniciar:
  - Compressas com álcool
  - Esparadrapo ou curativo antisséptico
  - Recipiente para materiais cortantes
- Se o frasco-ampola de **Voxzogo** e a seringa preenchida com diluente (água para injetáveis) tiverem sido armazenados no refrigerador, o frasco-ampola de **Voxzogo** e a seringa preenchida com diluente devem ser removidos do refrigerador para que atinjam a temperatura ambiente antes de reconstituir **Voxzogo**.
- A agulha do diluente deve ser conectada na seringa preenchida.
- Todo o volume do diluente deve ser injetado no frasco-ampola.
- O diluente no frasco-ampola deve ser misturado suavemente até o pó branco estar completamente dissolvido. O frasco-ampola não deve ser agitado.
- O volume da dose necessária de solução reconstituída deve ser lentamente retirado do frasco-ampola de uso único e transferido para a seringa.
- Depois de reconstituído, este medicamento é um líquido límpido, incolor a amarelo. A solução não deve ser usada se estiver descolorida ou turva, ou se houver partículas.
- Após a reconstituição, **Voxzogo** pode ser mantido no frasco-ampola em temperatura ambiente (entre 15°C e 30°C) durante um período máximo de 3 horas. O produto não contém conservantes.
- Para a administração, o volume da dose necessária de solução reconstituída deve ser extraído do frasco-ampola de uso único usando a seringa para aplicação fornecida na embalagem (vide Tabela 3).

### **Incompatibilidades**

Apenas a seringa para aplicação fornecida deve ser usada.

### **Descarte**

Qualquer medicamento não utilizado ou material residual deve ser descartado de acordo com os requisitos locais.

Todas as agulhas e seringas devem ser descartadas em um recipiente para descarte de materiais cortantes.

## 9. REAÇÕES ADVERSAS

O perfil de segurança de **Voxzogo** é baseado nos dados de estudos clínicos disponíveis.

As reações adversas mais comuns a **Voxzogo** foram reações no local da injeção (85%), vômitos (27%) e diminuição da pressão arterial (13%).

### Resumo tabulado de reações adversas

As reações adversas em pacientes tratados com **Voxzogo** estão tabuladas a seguir.

As reações adversas listadas a seguir são categorizadas por classe de sistema/órgão MedDRA e por frequência.

As frequências das reações adversas são categorizadas da seguinte forma: muito comum (>1/10), comum (>1/100 a ≤1/10), incomum (>1/1.000 a ≤1/100), rara (>1/10.000 a ≤1/1.000), muito rara (≤1/10.000), desconhecidas (frequência não pode ser estimada a partir dos dados disponíveis).

Dentro de cada grupo de frequência, as reações adversas são apresentadas em ordem decrescente de gravidade.

Tabela 4: Reações adversas em pacientes tratados com **Voxzogo**

Classe de sistema / órgão	Muito comum	Comum	Incomum
Distúrbios do sistema nervoso		Síncope	
		Pré-síncope	
		Tontura	
Distúrbios vasculares	Hipotensão <sup>a</sup>		
Distúrbios gastrointestinais	Vômito	Náusea	
Distúrbios da pele e do tecido subcutâneo			Hipertricose

Classe de sistema / órgão	Muito comum	Comum	Incomum
Distúrbios gerais e condições do local de administração	Reação no local da injeção <sup>b</sup>	Fadiga	
Investigações	Fosfatase alcalina elevada		

<sup>a</sup> Hipotensão inclui reações adversas assintomáticas e sintomáticas.

<sup>b</sup> Reações no local da injeção incluem os termos preferenciais: eritema no local da injeção, reação no local da injeção, inchaço no local da injeção, urticária no local da injeção, dor no local da injeção, hematoma no local da injeção, prurido no local da injeção, hemorragia no local da injeção, descoloração no local da injeção e endurecimento no local de injeção.

## Descrição das reações adversas selecionadas

### Hipotensão

No estudo ACH 111-301, 13% dos pacientes tratados com **Voxzogo** relataram eventos de reduções na pressão arterial, que foram temporários e resolvidos sem intervenção. O tempo mediano desde o aparecimento até a injeção foi de 31 (18 a 120) minutos, com resolução dentro de 31 (5 a 90) minutos. Os eventos relatados foram identificados predominantemente durante períodos de monitoramento frequente dos sinais vitais em consultas médicas após administração durante um período de tratamento de 52 semanas. Dois por cento (2%) dos pacientes apresentaram um episódio sintomático de tontura e vômito.

### Reações no local da injeção

Reações no local da injeção foram relatadas em 85% dos pacientes tratados com vosoritida em comparação com 82% dos pacientes tratados com placebo. Os pacientes que receberam esse medicamento e que apresentaram reações no local da injeção relataram uma mediana de 76 eventos, em comparação com pacientes que receberam placebo que relataram uma mediana de 7,5 eventos ao longo de um período de 52 semanas. As reações mais comuns no local da injeção (que ocorreram em pelo menos 10% dos pacientes tratados com vosoritida) foram reação no local da injeção (73%), eritema no local da injeção (68%), inchaço no local da injeção (38%) e urticária no local da injeção (13%). Todas as reações no local da injeção foram de Grau 1 (leve) em gravidade, com exceção de 5 eventos em dois pacientes que foram de Grau 2 (moderado). Os eventos de Grau 2 relatados incluíram: dois pacientes que relataram dois eventos de urticária no local da injeção e um evento de vesículas no local da injeção.

### **Imunogenicidade**

De 131 pacientes com 5 anos de idade ou mais com acondroplasia tratados com 15 mcg/kg/dia de vosoritida e avaliados quanto à presença de anticorpos antifármacos (ADA) por até 240 semanas, os ADA foram detectados em 35% dos pacientes. O primeiro momento para o desenvolvimento dos ADA foi no Dia 85. Todos os pacientes ADA-positivos tiveram resultados negativos para anticorpos neutralizantes antivósorítida. Não houve correlação entre o número, a duração ou a gravidade das reações adversas de hipersensibilidade ou reações no local da injeção e a positividade para ADA ou título médio de ADA. Não houve associação entre a positividade de ADA ou título médio de ADA e alteração a partir do valor basal na velocidade de crescimento anual (VCA) ou do escore Z de altura no Mês 12. Não houve impacto dos ADA séricos detectados nas medições farmacocinéticas (PK) plasmáticas de vosoritida.

Em pacientes menores de 5 anos de idade, 19% (8/43) dos pacientes tratados com vosoritida testaram positivo para ADA e todos os pacientes tratados com placebo testaram negativo para ADA. O primeiro momento para o desenvolvimento de ADA foi na Semana 26. Todos os pacientes positivos para ADA testaram negativo para anticorpos neutralizantes antifármacos (NAb) em todos os momentos. Não houve impacto do desenvolvimento de ADA na segurança, eficácia ou farmacocinética de vosoritida

### **População pediátrica**

O perfil de segurança de **Voxzogo** em estudos clínicos envolvendo crianças menores de 5 anos foi similar ao observado em crianças mais velhas (vide item “Resultados de Eficácia”).

**Atenção: Este produto é um medicamento novo e, embora as pesquisas tenham indicado eficácia e segurança aceitáveis, mesmo que indicado e utilizado corretamente, podem ocorrer eventos adversos imprevisíveis ou desconhecidos. Nesse caso, notifique os eventos adversos pelo Sistema VigiMed, disponível no Portal da ANVISA.**

## **10. SUPERDOSE**

Em estudos clínicos, as doses de vosoritida foram exploradas até 30 mcg/kg/dia. Dois pacientes receberam até 3 vezes a dose diária recomendada de 15 mcg/kg/dia por até 5 semanas. Não foram observados sinais, sintomas ou reações adversas associados à dose mais elevada do que a pretendida.

No caso de um paciente receber uma dose maior do que a estabelecida, deve-se entrar em contato com seu profissional de saúde.

**Em caso de intoxicação ligue para 0800 722 6001, se precisar de mais orientações.**

**DIZERES LEGAIS**

Registro: 1.7333.0005

**Importado por:**

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**USO SOB PRESCRIÇÃO**

**PROIBIDA VENDA AO COMÉRCIO**

**Esta bula foi aprovada pela ANVISA em 07/07/2025.**



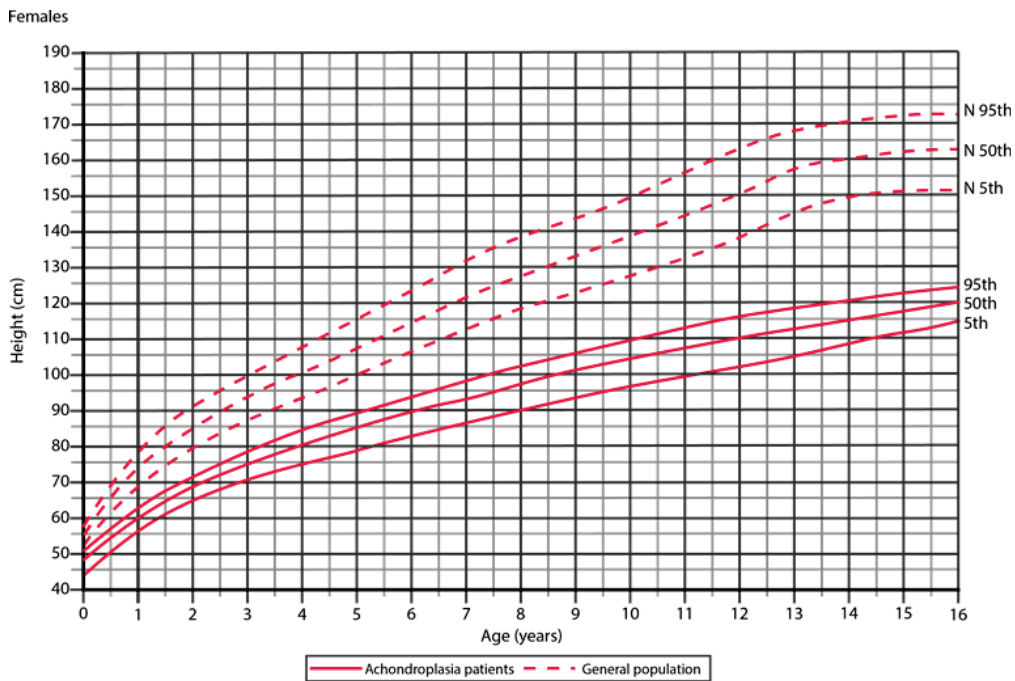
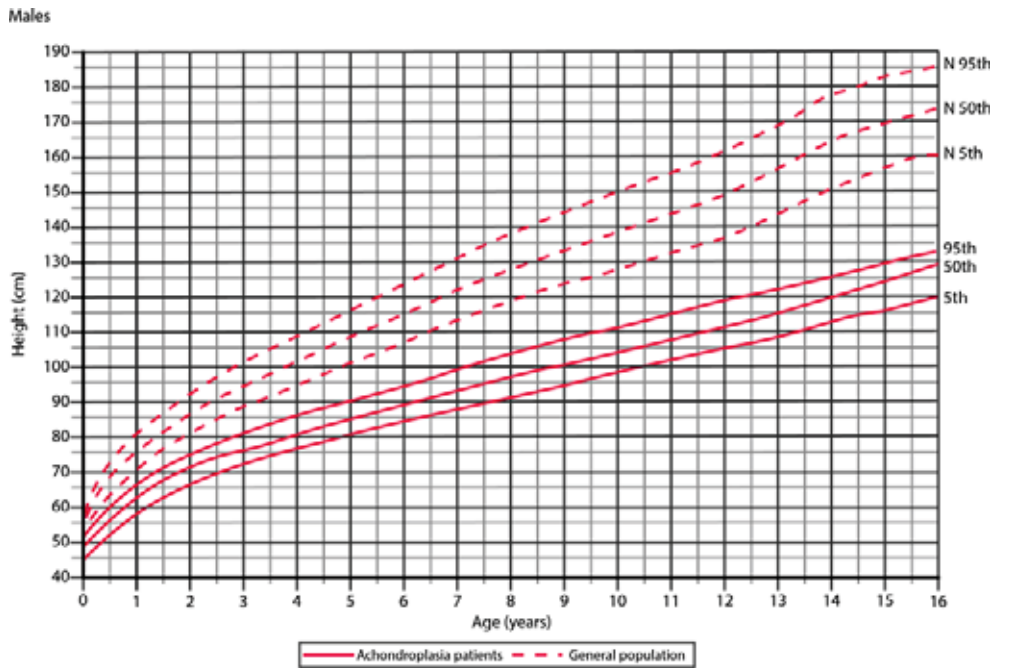
## 9.2. ANEXO II – Tabelas e figuras complementares

**Tabela 25. Características clínicas da acondroplasia**

CARACTERÍSTICA CLÍNICA	DESCRIÇÃO
Baixa estatura desproporcional	A altura final do adulto de pacientes com acondroplasia é substancialmente menor do que a média da população e, em média, os pacientes adultos de ambos os sexos têm um escore Z de altura de -5 a -7 [19]. Em pacientes com acondroplasia, a altura final do adulto é de cerca de 124 cm nas mulheres e 131 cm nos homens, em comparação com 163 cm nas mulheres e 176 cm nos homens para a população em geral [13, 14, 19]. A baixa estatura desproporcional torna-se mais definida à medida que os pacientes crescem e nem sempre é aparente em bebês que podem ter comprimentos dentro da faixa normal.
Membros curtos e desproporção rizomélica	O encurtamento rizomélico (desproporção do comprimento proximal dos membros ou da raiz dos membros) está uniformemente presente nos pacientes, embora possa variar em gravidade. Os pacientes costumam ter dobras cutâneas redundantes na parte superior do braço e nas coxas.
Macrocefalia	O tamanho da cabeça é geralmente grande no nascimento e permanece assim ao longo da vida. Os pacientes geralmente têm uma testa anormalmente pronunciada. A fontanela anterior é frequentemente grande na infância e pode persistir até que o paciente tenha 5–6 anos de idade.
Recuo médio-facial	Um subdesenvolvimento dos ossos cartilagosos na face resulta no achatamento de todo terço médio da face e uma ponte nasal plana, uma espinha nasal curta e anteversão do nariz.
Tórax pequeno	Pacientes com acondroplasia costumam ter um tórax menor do que a média. As costelas são excessivamente flexíveis, causando movimento paradoxal com inspiração.
Cifose toracolombar	Praticamente todos os pacientes desenvolvem uma cifose toracolombar dinâmica (curvatura anterior da parte superior das costas) na primeira infância.
Hiperlordose lombar	Uma lordose exagerada (curva interna da coluna) surge quando começam a andar.
Extensão limitada do cotovelo	Os cotovelos dos pacientes são rígidos e podem piorar progressivamente com a idade.
Dedos curtos e configuração tridente da mão	Uma configuração tridente da mão refere-se a uma separação entre os dedos médio e anular.
Quadril/ joelhos hiper móveis	Os pacientes têm quadril e/ ou joelhos que se movem facilmente além da faixa esperada.
Pernas arqueadas	A curvatura não é congênita e geralmente surge na primeira infância no segmento mesial das pernas, onde pode progredir em uma taxa e extensão imprevisíveis até que o crescimento seja completo.
Hipotonia	A maioria dos bebês com acondroplasia tem tônus muscular diminuído. A combinação de hiper mobilidade e hipotonia pode fazer bebês com acondroplasia parecerem "moles".

Fonte: Pauli (2019) [1].

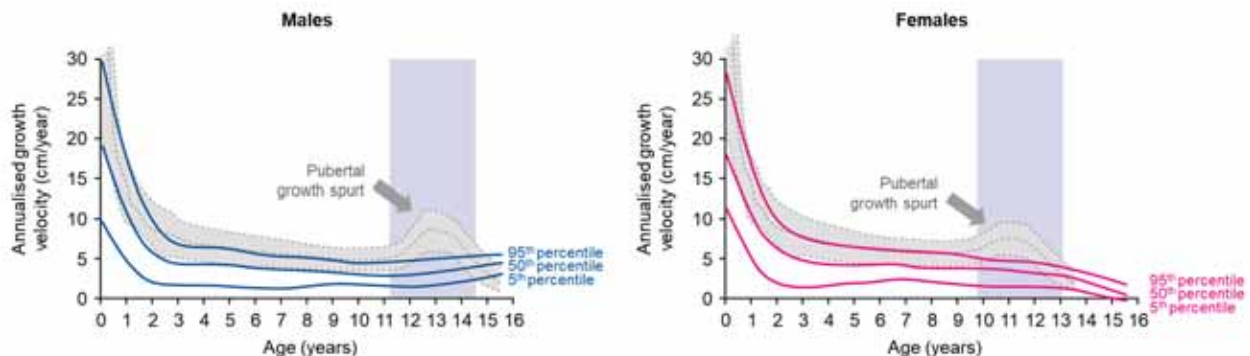
**Figura 34. Altura para a idade em pacientes com acondroplasia dos EUA em comparação com indivíduos de estatura mediana**



Quinto, 50° e 95° percentis de altura para crianças com acondroplasia (linhas contínuas) em comparação com curvas de crescimento de altura para a população em geral (linhas pontilhadas), com base em observações de 1955 de 162 meninos e 131 meninas com acondroplasia.  
 Abreviações: EUA: Estados Unidos da América.  
 Fonte: Hoover-Fong et al (2018) [148].



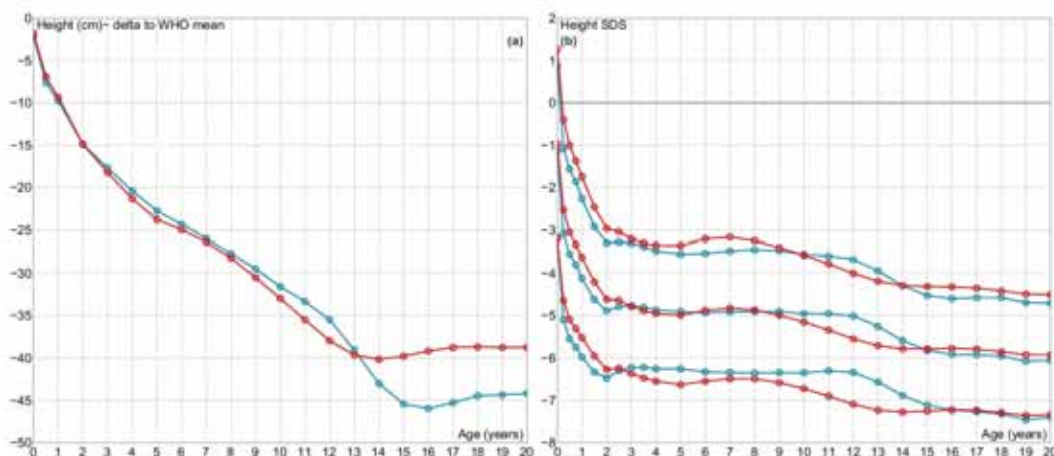
**Figura 35. Velocidade de crescimento anual para crianças com acondroplasia versus pacientes de estatura mediana**



Legenda: linha cheia para crescimento de crianças com acondroplasia e linha tracejada para crianças de estatura mediana

Fonte: Hoover-Fong et al (2008) [15].

**Figura 36. Evolução da altura em indivíduos com acondroplasia em comparação com a população geral (referência da OMS): expressa em (a) perda de altura em cm e (b) perda de altura em DP de escore Z de altura, média ±2 DP**

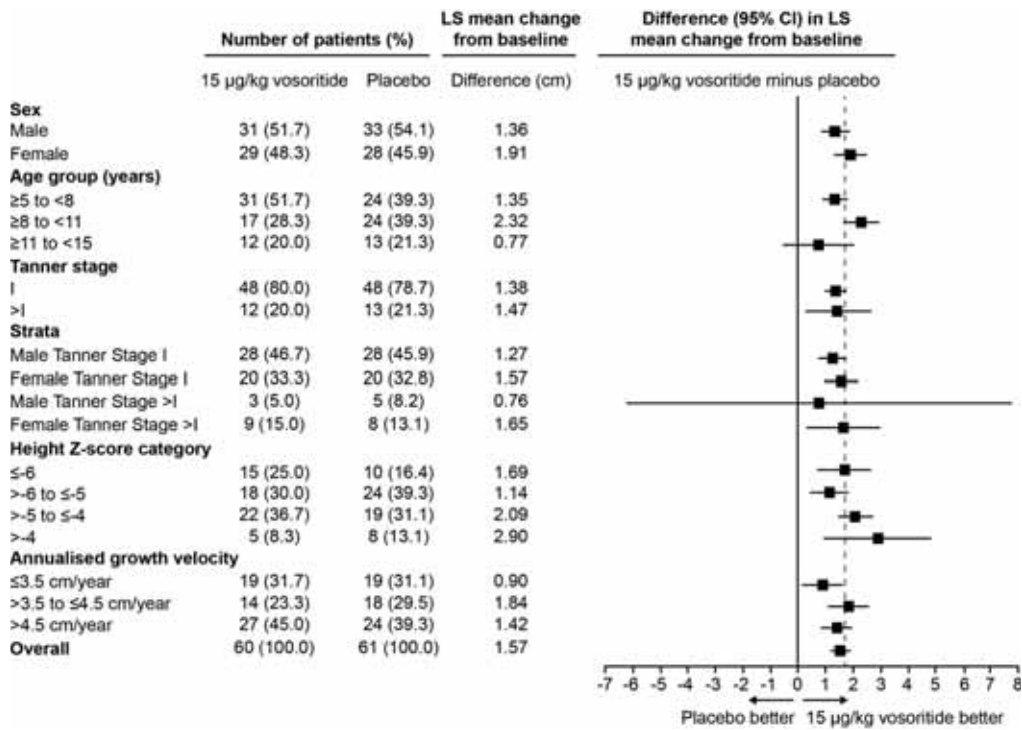


Legenda: linha vermelha para meninas e linha azul para meninos

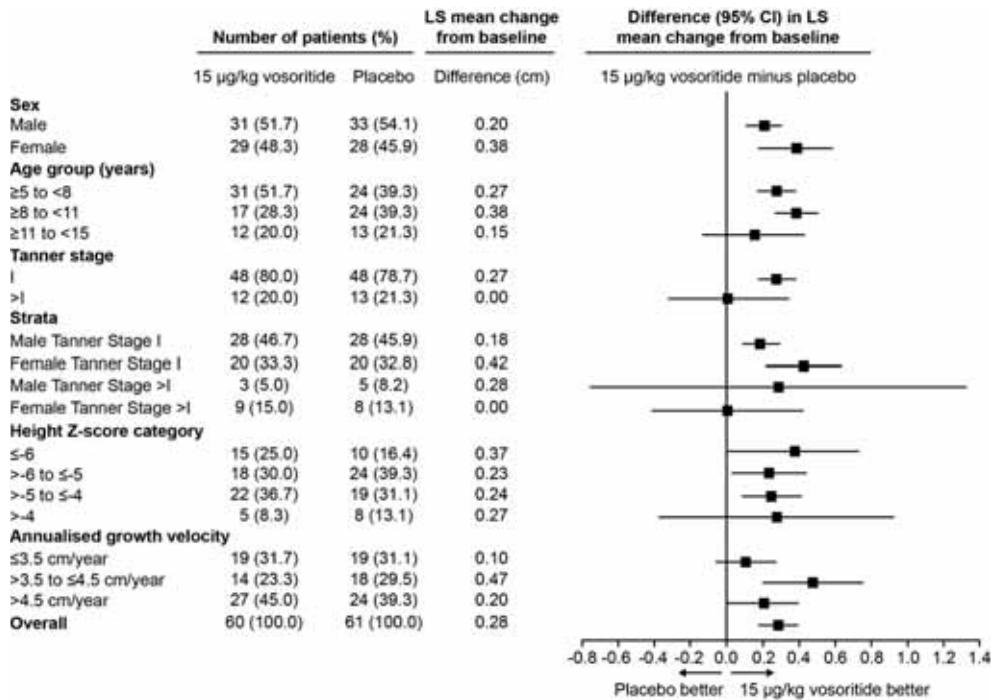
Fonte: Merker et al., 2018 [19]



**Figura 36. Alteração média de LS da linha de base na velocidade de crescimento anualizada (VCA) na Semana 52 por subgrupo de pacientes**



**Figura 37. Alteração média de LS da linha de base no escore Z de altura na semana 52 por subgrupo de pacientes**



Abreviações: IC: intervalo de confiança; LS: média dos mínimos quadrados.

**Tabela 26. Prevalência combinada de acondroplasia no nascimento para várias regiões**

REGIÃO	PREVALÊNCIA COMBINADA DE NASCIMENTOS*/ 100.000 (IC DE 95%)	ESTUDOS INCLUÍDOS	ESTIMATIVAS INCLUÍDAS	ÍNDICE DE QUALIDADE **
Mundial (geral)	4,6 (3,9 - 5,4)	52	90	23,0
Mundial (atendimento especializado) ***	13,3 (5,3 - 24,6)	14	14	30,2
Mundial (outro) ‡	4,2 (3,5 - 4,9)	38	76	18,8
América do Norte	4,2 (3,5 - 5,0)	9	15	52,5
América do Sul	3,5 (2,1 - 5,3)	5	6	11,0
Europa	3,5 (3,0 - 4,2)	13	40	14,5
África do Norte e Oriente Médio	35,1 (14,9 - 63,0)	13	13	18,6
África Subsaariana	17,9 (3,0 - 42,8)	5	5	65,4
Sul/ Sudeste Asiático e Oceania	5,9 (2,9 - 10,0)	11	11	33,1

\* Um modelo de efeitos de qualidade usado.

\*\* A classificação da qualidade do estudo para o modelo de efeitos de qualidade foi realizada da seguinte forma: para cada questão da ferramenta de avaliação de qualidade, dois pontos foram alocados quando o estudo marcou "forte", um ponto quando o estudo marcou "moderado" e zero pontos quando o estudo marcou "fraco". A soma dos escores individuais foi determinada e normalizada para um valor entre 0 (mais fraco) e 1 (mais forte), dividindo pelo escore máximo possível (8). O índice de qualidade, que é calculado para cada análise, expressa a extensão (%) em que os pesos são redistribuídos pela aplicação dos pesos do efeito de qualidade.

\*\*\* Mulheres que deram à luz em um ambiente de atendimento especializado (ou seja, centro de referência ou hospital terciário).

‡Mulheres que deram à luz em outros ambientes (ou seja, que não sejam um centro de referência ou hospital terciário).

Abreviações: IC: intervalo de confiança.

Fonte: Foreman et al (2020) [3].

**Tabela 27. Recomendações sobre o diagnóstico, segundo sociedades nacionais e internacionais**

SOCIEDADE	DIAGNÓSTICO PRÉ-NATAL	DIAGNÓSTICO APÓS O NASCIMENTO
American Academy of Pediatrics [148]	Investigar a presença de baixa estatura nos pais. Diagnóstico usando ultrassonografia (>26 semanas) e teste molecular (amostra de vilo coriônica [11–13 semanas]; amniocentese [> 15 semanas]).	Diagnóstico em recém-nascidos com base em estudos radiográficos e testes moleculares; as características físicas externas podem não ser óbvias. Diagnóstico desde a infância e além com base em radiografias e exame físico. A confirmação molecular deve ser oferecida aos pais, que optam pela realização ou não.
Sociedade brasileira de pediatria	Investigar a presença de baixa estatura nos pais. Avaliação ultrassonográfica para aferir o tamanho do feto e verificar se há encurtamento ósseo. Diagnóstico pode ser confirmado por testes moleculares usando procedimentos invasivos como a	Diagnóstico em recém-nascidos com base em exames de raio-X. Ressonância magnética pode ser realizada para avaliar a magnitude de complicações, como estreitamento de forame magno. Teste molecular pode ser realizado para confirmar o diagnóstico.



	<p>amniocentese e biópsia de vilo corial.</p> <p>Além disso, o teste molecular tem uma aplicação direta no caso de gestações em que algum dos pais seja afetado.</p>	
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**Tabela 28. Tratamentos e cuidados médicos indicados pela Sociedade Brasileira de Pediatria no tratamento da acondroplasia**

Categoria	Tratamento	Detalhes
<b>Baixa Estatura</b>	Vosoritida	Análogo do peptídeo natriurético tipo C (CNP), aumenta a velocidade de crescimento anualizada, através de injeção diária.
	Tratamento Cirúrgico com Alongamento de Extremidades	Melhora a proporção corporal, função e autoestima. Porém a tomada de decisão em proporcionar o aumento da estatura nestes indivíduos é difícil e controversa. Trata-se de procedimento demorado, complexo e acompanhado de inúmeras complicações.
<b>Terapêutica da Dor</b>	Analgesia Básica	Inclui paracetamol e anti-inflamatórios não esteroidais (AINEs).
	Opioides	Utilizados para dor aguda média a grave, exemplos incluem morfina e tramadol.
	Adjuvantes	Incluem gabapentinoides, agonistas alfa-2-adrenérgicos, antidepressivos tricíclicos, bloqueadores dos canais NMDA e de sódio.
<b>Cuidados Anestésicos</b>	Avaliação Pré-operatória	Inclui avaliação das vias aéreas, coluna espinhal, sistema respiratório e cardiovascular, devido às complicações da acondroplasia.
	Procedimentos Anestésico-Cirúrgicos Mais Frequentes	Os procedimentos cirúrgicos mais comuns em indivíduos com acondroplasia são otorrinolaringológicos (adenoamigdalectomia e timpanoplastia), neurocirúrgicos (derivação ventrículo-peritoneal e descompressão suboccipital) e ortopédicos (cirurgias de coluna, correção de genu varo e alongamento de membros). Em mulheres com acondroplasia, também são realizadas abordagens obstétricas.
	Condução da Anestesia	Pode ser geral ou regional, com atenção especial à abordagem das vias aéreas e ao risco de compressão medular cervical.
	Anestesia Obstétrica	Existe uma preferência por cesariana devido à desproporção cefalopélvica. Anestesia geral ou regional, dependendo das condições da paciente.

<b>Cuidados Obstétricos</b>	Avaliação Pré-natal	Exclui displasias esqueléticas letais e inclui aconselhamento genético.
	Via de Parto	Preferência por cesariana eletiva devido à desproporção cefalopélvica e macrocefalia fetal.
<b>Obesidade</b>	Orientação Nutricional	Redução da ingestão energética total e melhora da qualidade dos alimentos consumidos.
	Redução do Sedentarismo	Reabilitação regular e promoção da atividade física.
	Investigação de Componentes da Síndrome Metabólica	Inclui avaliação da pressão arterial, perfil lipídico, glicemia e doença hepática não alcoólica.
<b>Orientação para Esportes</b>	Esportes Recomendados	Natação, ciclismo e Pilates, que exercem pouca pressão na coluna.
	Esportes a Evitar	Corridas de longa distância e esportes de contato devido ao risco de impacto repetido na coluna.
<b>Educação Inclusiva e Socialização</b>	Intervenção Precoce	Garantir qualidade de vida e inclusão social desde cedo.
	Acompanhamento Multidisciplinar	Prevenção e gerenciamento de complicações, melhoria da qualidade de vida e promoção da independência.
<b>Cuidados Neonatais</b>	Diagnóstico ao Nascimento	Baseado em características clínicas e radiológicas.
	Avaliação e Monitoramento	Inclui medidas antropométricas, avaliação da sucção e deglutição, e monitoramento de apneia do sono.

**Tabela 29. Etapas práticas e considerações para iniciar e monitorar o tratamento**

Item	Ações	Considerações-chave
<b>Primeiro contato e/ou triagem</b>	Encaminhar para centro especializado assim que a suspeita de diagnóstico de acondroplasia for levantada	Importância do tratamento precoce; geralmente é necessário confirmação genética; conscientização sobre condições subjacentes; identificar e gerenciar complicações
<b>Educação e consentimento</b>	Fornecer aconselhamento sobre acondroplasia e opções de tratamento na primeira oportunidade	Inclusão de pacientes na tomada de decisão de tratamento de forma apropriada para a idade; discutir a opção de vosoritida com todos os pacientes elegíveis; apoiar pacientes que decidirem não seguir com vosoritida; educar pacientes e cuidadores sobre os requisitos de uso do medicamento e possíveis benefícios e efeitos adversos antes do consentimento para o tratamento
<b>Gestão de expectativas</b>	Estabelecer expectativas realistas antes do início do tratamento	As expectativas devem ser revisadas durante o tratamento; aconselhamento deve estar disponível para adolescentes que não são elegíveis para o tratamento
<b>Requisitos mínimos de recursos</b>	Garantir acesso do prescritor a um centro de referência especializado e que um plano de acompanhamento esteja em vigor	O prescritor deve ser um especialista médico experiente no manejo da acondroplasia ou outro profissional de saúde em consulta com um especialista experiente no manejo da acondroplasia; incentivar o acesso do paciente e do cuidador à comunidade de displasias esqueléticas; garantir que o prescritor tenha recursos apropriados para gerenciar e/ou coordenar o processo de prescrição



<p><b>Treinamento de injeção e primeira dose</b></p>	<p>Educar e treinar cuidadores e pacientes sobre técnicas de injeção, manejo da dor, hipotensão, reações no local da injeção e compromisso com injeções diárias</p>	<p>Estabelecer a injeção como prática de rotina; supervisionar a administração da primeira dose e disponibilizar equipe de enfermagem e médica por 1 hora após a primeira dose; múltiplas sessões de treinamento de injeção podem ser necessárias para permitir a injeção sem a presença de um enfermeiro; pacientes e cuidadores devem ter a capacidade de se comunicar com o centro de referência especializado por telefone, teleconsulta e/ou e-mail</p>
<p><b>Acompanhamento precoce</b></p>	<p>Considerar uma ligação inicial de acompanhamento por um enfermeiro cerca de 1 semana após o início para abordar considerações práticas</p>	<p>O acompanhamento precoce deve ser individualizado para cada situação familiar específica; agendar uma consulta de acompanhamento dentro do primeiro mês, incluindo discussão sobre o gerenciamento do fornecimento de medicamentos</p>
<p><b>Monitoramento da terapia</b></p>	<p>Apoiar pacientes com decisões de tratamento contínuas e motivação</p>	<p>O centro especializado deve organizar o acompanhamento, delegando a centros colaboradores e profissionais de saúde conforme necessário</p>
<p><b>Resposta ao tratamento</b></p>	<p>Discutir metas de tratamento com o paciente e cuidadores para definir um alvo de resposta personalizado</p>	<p>A resposta à vosoritida pode variar em magnitude e tempo; investigar outras comorbidades que possam afetar o crescimento se um paciente não estiver respondendo no prazo esperado; se a baixa adesão ao tratamento for suspeita pelo profissional de saúde, aumentar a frequência do acompanhamento e avaliar a motivação para continuar o tratamento é recomendado</p>
<p><b>Interrupção do tratamento</b></p>	<p>Realizar radiografia quando a velocidade de crescimento anual diminuir para &lt;1,5 cm por ano para verificar o status das placas de crescimento; se fechadas,</p>	<p>A radiografia pode ser realizada a cada 1-2 anos durante a puberdade para confirmar que as placas de crescimento permanecem abertas; consultar as recomendações 56-62 para considerações adicionais sobre</p>

	interromper o tratamento com vosoritida	a cessação do tratamento; se um paciente estiver passando por cirurgia, a equipe cirúrgica deve entrar em contato com o prescritor principal e/ou centro especializado para aconselhamento sobre a interrupção temporária do tratamento com vosoritida
<b>Monitoramento contínuo após a cessação do tratamento</b>	Desenvolver um plano de transição claro para o monitoramento contínuo na idade adulta após a cessação do tratamento com vosoritida e discutir o gerenciamento de saúde a longo prazo	A saúde da coluna deve continuar a ser monitorada após a cessação do vosoritida de acordo com o padrão de cuidado

**Tabela 30. Avaliações práticas recomendadas para monitoramento em diferentes faixas etárias**

Idade do paciente (anos)	Intervalos de acompanhamento de rotina (meses)	Avaliações devem incluir
0–2	3	Revisões de peso e dose; Comprimento, peso e circunferência da cabeça; Avaliação do desenvolvimento e neurológica Monitoramento de efeitos adversos; Monitoramento de medicamentos concomitantes; Resultados relatados pelo paciente, quando viável
3–5	4–6	Altura sentado e em pé; Avaliação do desempenho funcional (por exemplo, via WeeFIM); Monitoramento de efeitos adversos; Monitoramento de medicamentos concomitantes; Resultados relatados pelo paciente, quando viável
>5	6	Triagem para dor e fadiga (por exemplo, STEMS); Avaliação do desempenho funcional (por exemplo, ASK); Estágio de Tanner (a partir de uma idade apropriada); Monitoramento de efeitos adversos; Monitoramento de medicamentos concomitantes; Resultados relatados pelo paciente, quando viável; Se preocupações clínicas forem identificadas em relação a aspectos psicossociais e/ou qualidade de vida, considerar a avaliação da qualidade de

		vida (por exemplo, via PHQ-9, PedsQL ou APLES)
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Figura 37. Alteração média de LS da linha de base na velocidade de crescimento anualizada (VCA) na Semana 52 por subgrupo de pacientes

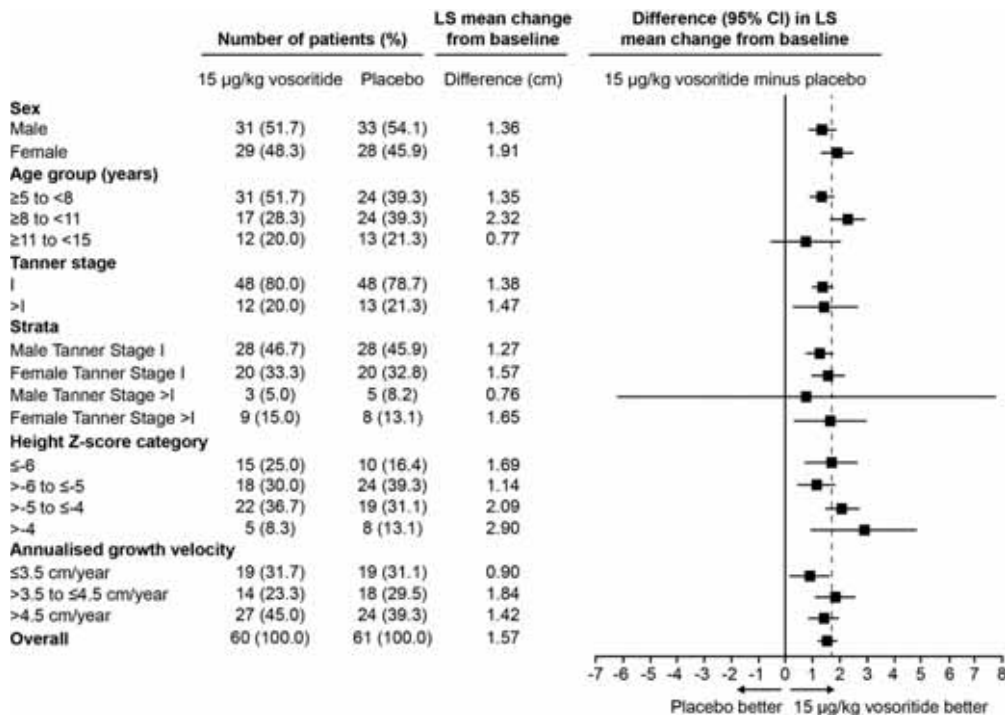
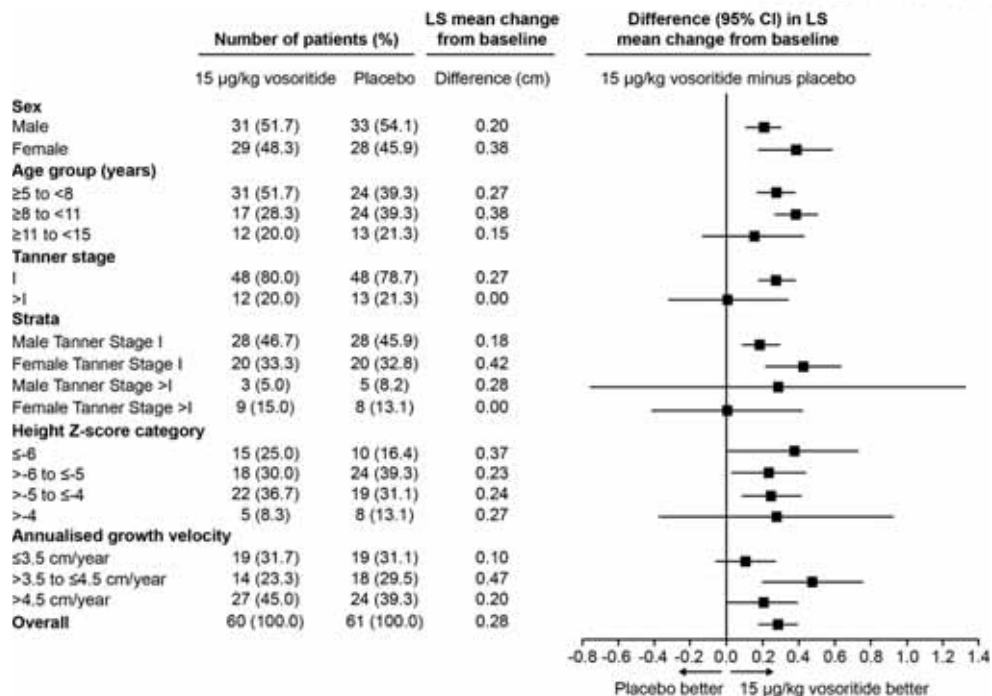


Figura 38. Alteração média de LS da linha de base no escore Z de altura na semana 52 por subgrupo de pacientes



Abreviações: IC: intervalo de confiança; LS: média dos mínimos quadrados.

**Tabela 31. Eventos adversos no estudo 111-301**

	PLACEBO		Vosoritida	
	INCIDÊNCIA*	TAXA DE EVENTO†	INCIDÊNCIA*	TAXA DE EVENTO†
Exposição total ao tratamento, pessoa-ano		60,93		57,99
Pacientes com evento de interesse especial				
Fraturas	0	0	1 (2%)	1 (0,02)
Epífise femoral capital escorregada	0	0	0	0
Necrose avascular ou osteonecrose	0	0	0	0
Pacientes com qualquer evento adverso grave	4 (7%)	5 (0,1)	3 (5%)	4 (0,1)
Gripe	0	0	1 (2%)	1 (0,02)
Apendicite	1 (2%)	1 (0,02)	0	0
Fratura de radio	0	0	1 (2%)	1 (0,02)
Hipertrofia adenoidal	1 (2%)	1 (0,02)	1 (2%)	1 (0,02)
Síndrome de apnéia do sono	0	0	1 (2%)	1 (0,02)

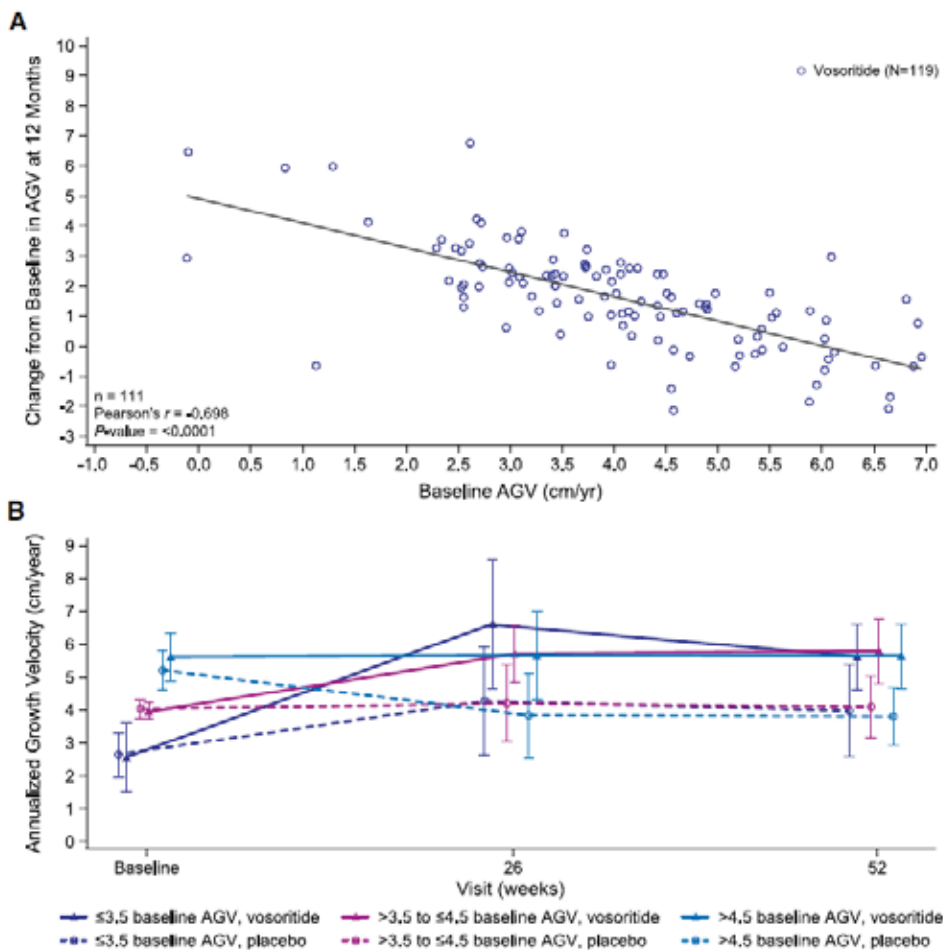


Dispneia	1 (2%)	1 (0,02)	0	0
Pressão intracraniana aumentada	1 (2%)	1 (0,02)	0	0
Compressão da medula espinhal	1 (2%)	1 (0,02)	0	0
Pacientes com qualquer evento adverso	60 (98%)	2121 (34,8)	59 (98%)	7345 (126,7)
Reação no local de injeção	29 (48%)	229 (3,8)	44 (73%)	2280 (39,3)
Eritema no local da injeção	40 (66%)	1215 (19,9)	41 (68%)	3987 (68,7)
Edema no local da injeção	6 (10%)	53 (0,9)	23 (38%)	322 (5,6)
Nasofaringite	18 (30%)	29 (0,5)	16 (27%)	26 (0,4)
Vômito	12 (20%)	16 (0,3)	16 (27%)	25 (0,4)
Dor de cabeça	16 (26%)	30 (0,5)	14 (23%)	23 (0,4)
Pirexia	13 (21%)	22 (0,4)	10 (17%)	11 (0,2)
Artralgia	4 (7%)	7 (0,1)	9 (15%)	11 (0,2)
Urticária no local de injeção	2 (3%)	5 (0,1)	8 (13%)	71 (1,2)
Infecção do trato respiratório superior	10 (16%)	12 (0,2)	8 (13%)	8 (0,1)
Pressão arterial diminuiu	3 (5%)	3 (0,05)	7 (12%)	10 (0,2)
Tosse	8 (13%)	10 (0,2)	7 (12%)	8 (0,1)
Diarréia	2 (3%)	2 (0,03)	6 (10%)	8 (0,1)
Infecção na orelha	6 (10%)	6 (0,1)	6 (10%)	8 (0,1)
Dor de ouvido	3 (5%)	3 (0,05)	6 (10%)	11 (0,2)
Gripe	3 (5%)	3 (0,05)	6 (10%)	8 (0,1)
Dor orofaríngea	4 (7%)	4 (0,1)	6 (10%)	13 (0,2)
Inflamação na orelha	6 (10%)	9 (0,1)	6 (10%)	7 (0,1)

\* As porcentagens foram calculadas usando o número total de pacientes na população de segurança (n para cada grupo de tratamento) como denominador. Pacientes com mais de um evento adverso do mesmo termo preferido foram contados apenas uma vez para esse termo preferido. † As taxas de eventos ajustadas à exposição foram calculadas dividindo o número total de eventos (m) pela exposição total ao tratamento em cada grupo de tratamento. Múltiplas ocorrências de um evento adverso com o mesmo termo preferido para um paciente foram contadas para cada ocorrência desse termo preferido.



**Figura 39. Associação entre a velocidade de crescimento anualizada (VCA) basal e a mudança da VCA basal em participantes tratados com vosoritida**



(A) Mudança na velocidade média de crescimento anualizada em 12 meses em participantes em tratamento com vosoritida (conjunto de análise completa 111-302) versus VCA basal.

(B) Velocidade média (DP) de crescimento anualizada basal, 6 meses e 12 meses por VCA basal para em pacientes em tratamento com vosoritida versus placebo (conjunto de análise completa 111-301). VCA, velocidade de crescimento anualizada.

**Figura 40. Incidência de eventos adversos emergentes do tratamento por termo preferido (>10% de incidência geral) no estudo 111-206**

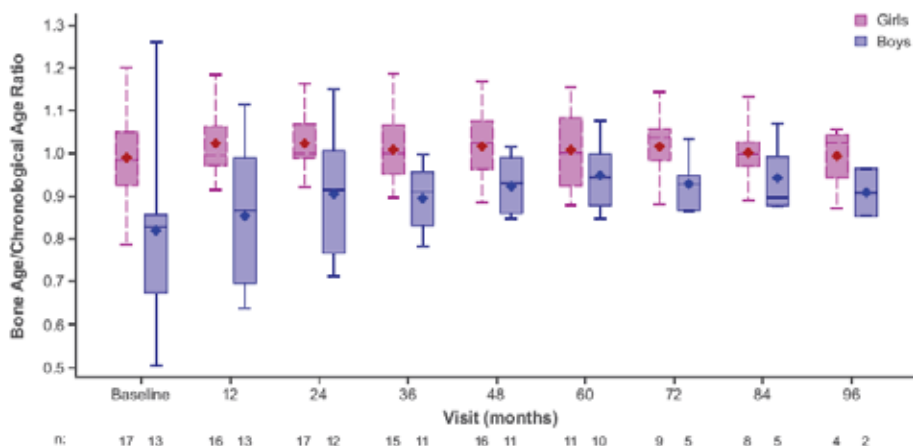
Evento Adverso	Placebo (n=32; exposição total ao tratamento 32,03 anos-pessoa)	Vosoritida (n=32; exposição total ao tratamento 31,63 anos-pessoa)	Participantes Sentinelas Recebendo Vosoritida (n=11; exposição total ao tratamento 11,10 anos-pessoa)	Todos Vosoritida (n=43; exposição total ao tratamento 42,73 anos-pessoa)
Participantes com qualquer evento adverso grave	6 (19%)	3 (9%)	0	3 (7%)
Participantes com qualquer evento adverso	32 (100%)	32 (100%)	11 (100%)	43 (100%)
Reação no local da injeção	13 (41%)	26 (81%)	8 (73%)	34 (79%)
Eritema no local da injeção	13 (41%)	25 (78%)	8 (73%)	33 (77%)
Febre	19 (59%)	14 (44%)	2 (18%)	16 (37%)
Vômito	17 (53%)	5 (16%)	6 (55%)	11 (26%)
Infecção do trato respiratório superior	11 (34%)	12 (38%)	4 (36%)	16 (37%)
Dentição	10 (31%)	8 (25%)	4 (36%)	12 (28%)
Nasofaringite	9 (28%)	7 (22%)	5 (45%)	12 (28%)
Diarreia	7 (22%)	7 (22%)	1 (9%)	8 (19%)
Infecção no ouvido	6 (19%)	5 (16%)	3 (27%)	8 (19%)
Rinorreia	6 (19%)	6 (19%)	2 (18%)	8 (19%)
Conjuntivite	6 (19%)	6 (19%)	0	6 (14%)
Congestão nasal	6 (19%)	5 (16%)	1 (9%)	6 (14%)
Otite média	6 (19%)	4 (13%)	2 (18%)	6 (14%)
Infecção viral	4 (13%)	5 (16%)	3 (27%)	8 (19%)
Tosse	7 (22%)	3 (9%)	1 (9%)	4 (9%)
Hematoma no local da injeção	6 (19%)	4 (13%)	1 (9%)	5 (12%)
Erupção cutânea	4 (13%)	4 (13%)	3 (27%)	7 (16%)
Queda	3 (9%)	3 (9%)	4 (36%)	7 (16%)
Inchaço no local da injeção	2 (6%)	7 (22%)	1 (9%)	8 (19%)
Picada de artrópode	2 (6%)	6 (19%)	0	6 (14%)
Dor no ouvido	4 (12,5%)	2 (6%)	2 (18%)	4 (9%)
Gastroenterite	5 (16%)	2 (6%)	1 (9%)	3 (7%)



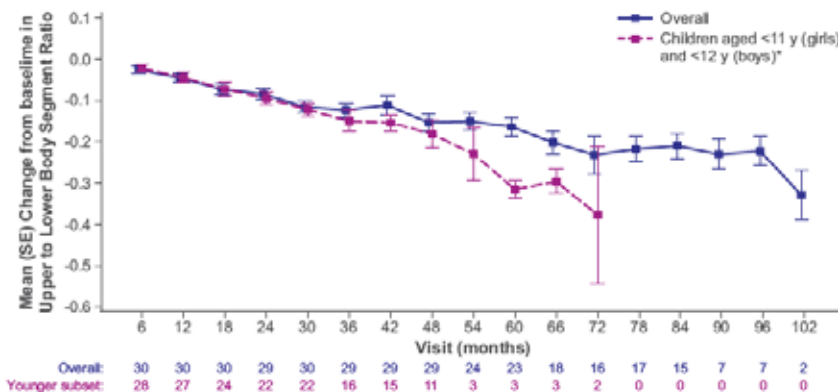
**Tabela 32. Número de Eventos Adversos no estudo de Cormier-Daire e colaboradores [131]**

Classe de Sistema de Órgãos/Termo Preferido	Número de Eventos
Todos os eventos adversos	21
Reação no local da injeção	14
- Eritema no local da injeção	4
- Pápula no local da injeção	3
- Rash no local da injeção	4
- Dor no local da injeção	2
- Inchaço no local da injeção	1
Distúrbios gastrointestinais	3
- Vômito	3
Distúrbios da pele e do tecido subcutâneo	2
- Dermatite de contato	1
- Eritema	1
Distúrbios do sistema nervoso	2
- Dor de cabeça	1
- Pré-síncope	1

**Figura 41. Nenhuma aceleração da idade óssea com o tratamento com vosoritida, Hoover-Fong et al., 2024**



**Figura 42. As proporções do segmento corporal superior para o inferior continuaram a diminuir ao longo do tempo. Hoover-Fong et al., 2024**





**Tabela 33. Resumo das complicações, das intervenções associadas e respectivos custos, incluídas no modelo**

Complicação	Intervenção	Evento	Fonte
Estenose do forame magno	Cirurgia de descompressão	R\$ 5,738.67	SIH, procedimento 0403010039 CRANIOTOMIA DESCOMPRESSIVA DA FOSSA POSTERIOR
Hidrocefalia	Inserção de shunt	R\$ 5,557.41	SIH, procedimentos 0403010080 DERIVACAO RAQUE-PERITONEAL, 0403010098 DERIVACAO VENTRICULAR EXTERNAR-SUBGALEAL EXTERNA, 0403010101 DERIVACAO VENTRICULAR PARA PERITONEO / ATRIO / PLEURA / RAQUE
Apneia do sono	Adenotonsilectomia	R\$ 416.98	SIH, procedimento 0404010024 AMIGDALECTOMIA, 0404010032 AMIGDALECTOMIA COM ADENOIDECTOMIA
Estenose espinal	Laminectomia	R\$ 5,738.67	SIH, procedimento 0403010039 CRANIOTOMIA DESCOMPRESSIVA DA FOSSA POSTERIOR
Cifose	Fusão espinal	R\$ 6,480.36	SIH, procedimentos 0408030020 ARTRODESE CERVICAL / CERVICO-TORACICA POSTERIOR UM NIVEL, 0408030038 ARTRODESE CERVICAL / CERVICO-TORACICA POSTERIOR DOIS NIVEIS, 0408030046 ARTRODESE CERVICAL / CERVICO-TORACICA POSTERIOR SEIS NIVEIS, 0408030062 ARTRODESE CERVICAL ANTERIOR TRES NIVEIS, 0408030070 ARTRODESE CERVICAL ANTERIOR DOIS NIVEIS, 0408030089 ARTRODESE CERVICAL ANTERIOR C1-C2 VIA TRANS-ORAL / EXTRA-ORAL, 0408030119 ARTRODESE CERVICAL ANTERIOR UM NIVEL, 0408030127 ARTRODESE CERVICAL POSTERIOR C1-C2
Flexão das pernas	Osteotomia	R\$ 1,091.69	SIH, procedimento 0408060190 OSTEOTOMIA DE OSSOS LONGOS EXCETO DA MAO E DO PE
Doença cardiovascular	Evento de doença cardiovascular	R\$ 2,034.95	SIH, procedimento 0303040149 TRATAMENTO DE ACIDENTE VASCULAR CEREBRAL - AVC (ISQUEMICO OU HEMORRAGICO AGUDO), 0303060190 TRATAMENTO DE INFARTO AGUDO DO MIOCARDIO
Otite média	Timpanostomia	R\$ 669.88	SIH, procedimento 0404010350 TIMPANOPLASTIA (UNI / BILATERAL)
Má oclusão dentária	Cirurgia ortodôntica	R\$ 1,590.12	SIH, procedimento 0404030033 OSTEOTOMIA DE MAXILA EM PACIENTES COM ANOMALIA CRANIO E BUCOMAXILOFACIAL, 0404030050 OSTEOTOMIA DA MANDIBULA EM PACIENTE COM ANOMALIA CRANIO E BUCOMAXILOFACIAL

**Tabela 34. Parâmetros variados nas análises de sensibilidades**

Parâmetro	Caso Base	Análise de Sensibilidade
Horizonte de tempo, anos	Horizonte vitalício - horizonte de tempo depende da idade inicial	5 anos
Horizonte de tempo, anos	Horizonte vitalício - horizonte de tempo depende da idade inicial	10 anos
Horizonte de tempo, anos	Horizonte vitalício - horizonte de tempo depende da idade inicial	20 anos
Taxa de desconto (custos)	5,00%	0%
Taxa de desconto (custos)	5,00%	10%
Taxa de desconto (QALYs)	5,00%	0%
Taxa de desconto (QALYs)	5,00%	10%
Taxa de desconto (LYs, resultados clínicos)	5,00%	0%
Taxa de desconto (LYs, resultados clínicos)	5,00%	10%
Correção de meio ciclo	ON	OFF
Idade inicial (idade base)	7	0 anos
Idade inicial (idade base)	7	16 years
Idade de fusão da placa de crescimento	16	18
Idade de fusão da placa de crescimento	16	15
Sexo, % masculino	0.51%	0
Sexo, % masculino	0.51%	1
Custos de medicamentos, por ano - Vosoritida		Redução de 10%
Custos de medicamentos, por ano - Vosoritida		Aumento de 10%
Percentil de altura	0.5	0.1
Percentil de altura	0.5	0.2
Percentil de altura	0.5	0.3
Percentil de altura	0.5	0.4
Percentil de altura	0.5	0.5
Percentil de altura	0.5	0.6
Percentil de altura	0.5	0.7
Percentil de altura	0.5	0.8
Percentil de altura	0.5	0.9
Diferença média na VCA para idades de 0 a <2 anos e ≥2 e <5 anos	Baseado em FAS randomizado (0.63; 1.1)	Baseado em análises comparativas versus dados históricos naturais de ACH (2.62; 1.87)
Diferença média na VCA para todas as idades	Baseado em FAS randomizado (0.63; 1.1)	Aumento de 20%
Diferença média na VCA para todas as idades	Baseado em FAS randomizado (0.63; 1.1)	Redução de 20%
Probabilidade anual de descontinuação do tratamento	3%	0%
Probabilidade anual de descontinuação do tratamento	3%	3%
SMR elevado durante a infância (0 a 1 ano) para todos os pacientes com ACH vs população geral	6	Nenhuma diferença em relação à idade adulta
SMR elevado durante a infância (0 a 1 ano) para todos os pacientes com ACH vs população geral	6	Maior que o caso base (10)
Período de SMR elevado	Idades de 0 a 1	Idades de 0 a 5
SMR base para pacientes com ACH vs população geral	2	Nenhuma diferença em relação à população geral
SMR base para pacientes com ACH vs população geral	2	Maior que o caso base (4)



Risco relativo de mortalidade nos braços VOS vs BSC	Riscos de mortalidade do VOS estimados com base nas razões do escore Z de altura	SMR's (VOS vs GP) estimados com base no escore Z de altura
Risco relativo de mortalidade nos braços VOS vs BSC	Riscos de mortalidade do VOS estimados com base nas razões do escore Z de altura	Nenhuma diferença na mortalidade
Escolha do ajuste de regressão para Christensen 2007	Polinômio quadrático (caso base PBAC)	Ajuste linear para pontos entre HSDS -3 a -2 (caso base do modelo global)
Escolha do ajuste de regressão para Christensen 2007	Polinômio quadrático (caso base PBAC)	Ajuste linear para todos os pontos HSDS (caso base FINOSE)
Incremento adicional de utilidade ao atingir 150 cm	0.1	0
Incremento adicional de utilidade ao atingir 150 cm	0.1	0.2
Altura do incremento adicional de utilidade (cm)	150	140
Altura do incremento adicional de utilidade (cm)	150	160
Risco de complicações nos braços VOS vs BSC	Riscos de complicações com base nas razões do escore Z de altura	Nenhuma diferença entre os braços
Risco de complicações nos braços VOS vs BSC	Riscos de complicações com base nas razões do escore Z de altura	Não incluído, risco de 0%
Custos de eventos de complicações	Premissa	Aumento de 10% nos custos de eventos
Custos de eventos de complicações	Premissa	Redução de 10% nos custos de eventos
Desutilidades de eventos de complicações	Baseado em fontes literárias	Aumento de 25% nas desutilidades
Desutilidades de eventos de complicações	Baseado em fontes literárias	Redução de 25% nas desutilidades
Risco de custos indiretos nos braços VOS vs BSC	Riscos de complicações com base nas razões do escore Z de altura	Nenhuma diferença entre os braços
Desutilidade do cuidador - desutilidade única	-0.07	Aumento de 10% nas desutilidades
Desutilidade do cuidador - desutilidade única	-0.07	Redução de 10% nas desutilidades
Risco de desutilidade do cuidador nos braços VOS vs BSC	Riscos de complicações com base nas razões do escore Z de altura	Nenhuma diferença entre os braços

**Tabela 35. Estimativa de nascidos vivos e população prevalente com acondroplasia para o ano de 2025 com idade menor que 18 anos**

Idade	Total de nascimentos vivos por ano		Referência	Pacientes com acondroplasia	
	Meninos	Meninas		Meninos	Meninas
<b>0</b>	1.374.314	1.440.908	Estimativa de nascidos vivos segundo tábua de IBGE para o ano de 2025	48	50
<b>1</b>	1.264.260	1.345.738	Estimativa de nascidos vivos segundo tábua de IBGE para o ano de 2024	44	47

<b>2</b>	1.180.835	1.142.524	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2023	41	40
<b>3</b>	1.190.348	1.153.915	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2022	42	40
<b>4</b>	1.242.638	1.204.891	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2021	43	42
<b>5</b>	1.267.513	1.226.770	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2020	44	43
<b>6</b>	1.320.341	1.281.249	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2019	46	45
<b>7</b>	1.366.150	1.321.507	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2018	48	46
<b>8</b>	1.356.337	1.310.545	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2017	47	46
<b>9</b>	1.323.816	1.281.943	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2016	46	45
<b>10</b>	1.396.848	1.353.444	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2015	49	47



<b>11</b>	1.380.026	1.333.714	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2014	48	47
<b>12</b>	1.343.085	1.300.639	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2013	47	46
<b>13</b>	1.341.009	1.302.409	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2012	47	46
<b>14</b>	1.344.851	1.302.672	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2011	47	46
<b>15</b>	1.319.908	1.277.581	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2010	46	45
<b>16</b>	1.324.740	1.286.090	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2009	46	45
<b>17</b>	1.349.611	1.309.519	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2008	47	46
<b>18</b>	1.330.415	1.289.169	MS/SVSA/CGIAE - Sistema de Informações sobre Nascidos Vivos - SINASC; Nascidos vivos de 2007	47	45

**Tabela 36. Incidência de acondroplasia**

		2027	2028	2029	2030
Nascidos vivos	Meninos	1,360,316	1,346,290	1,332,175	1,318,392
	Meninas	1,426,287	1,411,630	1,396,875	1,382,460
Pacientes com acondroplasia	Meninos	48	47	47	46
	Meninas	50	49	49	48

**Tabela 37. Recomendações de agências de ATS**

HAS, 2021, França	
Tipo de Recomendação	Positiva
População	Pacientes com acondroplasia com pelo menos 2 anos de idade em que as epífises dos ossos longos não estão fechadas. O diagnóstico deve ser confirmado por teste genético.
Justificativa	A acondroplasia é uma doença rara grave com complicações frequentes e diversas (p.ex., funcionais, respiratórias, neurológicas e psicológicas). A taxa de benefício clínico (eficácia) da vosoritida foi considerada alta. A vosoritida deve ser usada como parte da terapia de primeira linha, dada a falta de formas alternativas de terapia para acondroplasia disponíveis. A Comissão HAS recomenda o financiamento da vosoritida no nível de 65%. Com base em um ensaio clínico randomizado, foi demonstrada uma superioridade estatística e clinicamente significativa da vosoritida em comparação ao placebo – a taxa de crescimento anual foi de 1,57 cm/ano no grupo de estudo. Foi reconhecido que havia uma necessidade médica não atendida para o tratamento da acondroplasia, para a qual o único tratamento até o momento era o tratamento sintomático. A decisão foi tomada apesar de poucas evidências clínicas. O comitê HAS considera que a vosoritida fornece um benefício clínico moderado (CAV III) na via do paciente com acondroplasia em comparação ao tratamento médico atual em pacientes com 2 anos de idade ou mais nos quais as epífises dos ossos longos não estão fechadas.
Link	<a href="https://www.has-sante.fr/jcms/p_3313571/en/voxzogo-vosoritide">https://www.has-sante.fr/jcms/p_3313571/en/voxzogo-vosoritide</a>
G-BA, 2024, Alemanha	
Tipo de Recomendação	Avaliação positiva com benefício adicional imensurável
População	Pacientes com acondroplasia com pelo menos 2 anos de idade em que as epífises dos ossos longos não estão fechadas. O diagnóstico deve ser confirmado por teste genético.
Justificativa	Não houve benefício adicional mensurável da vosoritida sobre o melhor tratamento de suporte em pessoas com acondroplasia. Os resultados dos ensaios clínicos indicam um efeito significativo do tratamento com vosoritida na avaliação da taxa de crescimento em pacientes em comparação ao cuidado padrão. Não foram encontradas diferenças significativas entre os grupos na avaliação da qualidade de vida. O perfil de segurança foi considerado comparável.



	<p>A população-alvo foi estimada em cerca de 330-460 pacientes por ano elegíveis para tratamento com vosoritida.</p> <p>Foi enfatizado que o tratamento com vosoritida deve ser iniciado e monitorado por médicos experientes.</p> <p>No geral, a vosoritida demonstrou benefício clínico significativo no aumento da taxa de crescimento em crianças com acondroplasia sem afetar a mortalidade ou a qualidade de vida geral. No entanto, essa terapia gera altos custos e requer implementação e monitoramento rigorosos por especialistas.</p>
Link	<a href="https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/992/">https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/992/</a>
<b>G-BA, 2024<sup>a</sup>, Alemanha</b>	
Tipo de Recomendação	Avaliação positiva com benefício adicional não quantificável
População	<p>Pacientes com idade <math>\geq 4</math> meses a <math>&lt; 2</math> anos com acondroplasia e cujas epífises não estão fechadas.</p> <p>O diagnóstico de acondroplasia deve ser confirmado por testes genéticos apropriados.</p>
Justificativa	<p>O G-BA publicou a avaliação de benefício de uma nova indicação terapêutica para o ingrediente ativo vosoritida. A indicação terapêutica avaliada no documento compreende o tratamento de acondroplasia em crianças <math>\geq 4</math> meses a <math>&lt; 2</math> anos de idade cujas epífises ainda não estão fechadas. O G-BA determinou que o melhor tratamento de suporte é a terapia comparadora apropriada.</p> <p>Nas categorias de desfecho de morbidade e efeitos colaterais, não houve diferenças estatisticamente significativas entre os dois braços de tratamento. Em resumo, com base nos resultados do estudo 111-206 para crianças de 4 meses a <math>&lt; 2</math> anos de idade, não houve diferenças estatisticamente significativas entre vosoritida e o cuidado padrão.</p> <p>Na avaliação geral, o G-BA, portanto, identificou uma tendência para um benefício adicional não quantificável para vosoritida em crianças de 4 meses a <math>&lt; 2</math> anos de idade com acondroplasia em comparação com a terapia comparadora apropriada de cuidado padrão, levando em consideração os resultados de pacientes <math>\geq 2</math> anos de idade.</p>
Link	<a href="https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1018/">https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1018/</a>
<b>PBAC, 2022, Austrália</b>	
Tipo de Recomendação	Positiva
População	Pacientes com acondroplasia cujas epífises não estejam fechadas
Justificativa	<p>O PBAC recomendou a listagem da vosoritida para o tratamento de pacientes com acondroplasia cujas epífises não estão fechadas. O PBAC ficou satisfeito que o vosoritida fornece, para alguns pacientes, uma melhora significativa na eficácia em relação ao melhor tratamento de suporte (BSC). O PBAC reafirmou que não há tratamentos no sistema australiano disponíveis especificamente para essa condição e considerou que a adição de vosoritida ofereceu alto valor terapêutico agregado.</p> <p>O PBAC recebeu a contribuição de indivíduos e profissionais de saúde destacando o impacto de um aumento na altura final em termos de acesso ao ambiente, funcionalidade aprimorada e tolerância ao exercício, juntamente com o potencial de redução da dor e complicações médicas.</p> <p>O PBAC reafirmou sua visão de que havia uma alta necessidade clínica de</p>



	<p>tratamentos eficazes para acondroplasia.</p> <p>O PBAC, em julho de 2022, considerou que, com base em resultados de altura melhorados, a alegação de eficácia comparativa superior era razoável em crianças de 5 a &lt;18 anos e incerta, mas provavelmente razoável em crianças menores de 5 anos. O PBAC também reconheceu que dados adicionais do Estudo 111-206 para crianças de 0 a &lt;5 anos de idade, indicando um potencial efeito positivo da vosoritida além do crescimento linear, foram fornecidos na reenvio de setembro de 2022 e no Relatório de Estudo Clínico do Estudo 111-206.</p> <p>Especificamente, o PBAC concluiu que, nas circunstâncias de sua recomendação para a vosoritida:</p> <ul style="list-style-type: none"> <li>• espera-se que o tratamento forneça uma melhora substancial e clinicamente relevante na eficácia em relação ao placebo, com base nos ganhos de VCA e escore Z de altura observados no Estudo 111-301;</li> <li>• espera-se que o tratamento atenda a uma necessidade clínica alta e urgente não atendida na população proposta;</li> <li>• seria de interesse público que a aplicação de preços subsequente fosse progredida sob o “Caminho de Preços A” com base nos achados anteriores.</li> </ul> <p>O PBAC notou que esta submissão não é elegível a uma revisão independente pois recebeu uma recomendação positiva.</p>
Link	<a href="https://www.pbs.gov.au/medicinesstatus/search.html?question=VOSORITIDE&amp;sort=">https://www.pbs.gov.au/medicinesstatus/search.html?question=VOSORITIDE&amp;sort=</a>
AEMPS, 2024, Espanha	
Tipo de Recomendação	Positiva
População	
Justificativa	<p>Até a data de elaboração do parecer da AEMPS, a vosoritida foi considerada a única opção terapêutica autorizada na população pediátrica com um alvo nas bases etiopatogênicas da acondroplasia (uma doença genética rara), com resultados de eficácia e segurança de curto prazo (52 semanas).</p> <p>Em pacientes entre 5 e 18 anos de idade, a vosoritida demonstrou em um estudo clínico de Fase III de 52 semanas, comparado ao placebo, melhorar a velocidade de crescimento anualizada em 1,57 cm por ano. Outro estudo em pacientes com menos de 5 anos revelou, na semana 52, uma alteração no escore Z de altura de 0,25 (IC 95% -0,02 a 0,53) e um aumento na VAC de 0,78 cm/ano (IC 95% 0,02-1,54). Não foi observada melhora na qualidade de vida ou na avaliação funcional com o tratamento com vosoritida versus placebo.</p> <p>A vosoritida tem um perfil de segurança aceitável e o tratamento é geralmente bem tolerado com base nos dados de segurança de desenvolvimento clínico disponíveis. Os principais eventos adversos identificados durante o desenvolvimento clínico estão relacionados a reações no local da injeção, diminuição da pressão arterial, vômitos, náuseas, fadiga e aumento da fosfatase alcalina.</p> <p>Os estudos de extensão em andamento, tanto em pacientes com mais quanto com menos de 5 anos, fornecerão dados sobre o tamanho final do benefício e a segurança em longo prazo. O efeito do tratamento com vosoritida em outras comorbidades (estenose cervicomedular,</p>



	<p>deformidades, apneia, etc.) ainda precisa ser elucidado, assim como o efeito no surto de crescimento puberal e a eficácia em comparação com a cirurgia de alongamento de membros.</p> <p>Considera-se que os dados publicados sobre eficácia e segurança, principalmente na população de pacientes com menos de 5 anos de idade, são muito limitados, tanto em termos do número de pacientes estudados quanto da duração do acompanhamento.</p> <p>No entanto, dadas as opções limitadas de tratamento disponíveis para a acondroplasia, a vosoritida é postulado como a primeira escolha em pacientes com 4 meses de idade com essa doença rara, devido ao benefício clínico que proporciona na população estudada e ao perfil de segurança razoável.</p>
Link	<a href="https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2023/IPT-120-2023-Voxzogo.pdf">https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2023/IPT-120-2023-Voxzogo.pdf</a>
AIFA, 2022, Itália	
Tipo de Recomendação	Positiva
População	<p>Para o tratamento da acondroplasia em pacientes com dois anos de idade ou mais cujas epífises não estão fechadas.</p> <p>O diagnóstico de acondroplasia deve ser confirmado por análise genética apropriada</p>
Justificativa	<p>A decisão da AIFA levou em conta:</p> <ul style="list-style-type: none"> <li>• O pedido apresentado em 19 de novembro de 2021 pelo qual a empresa Biomarin International Limited solicitou a classificação, para fins de incorporação, do medicamento vosoritida;</li> <li>• O parecer emitido pelo Comitê Científico Comitê Consultivo Técnico e Científico em sua reunião de 10-12 de janeiro de 2022;</li> <li>• O parecer emitido pelo Comitê de Preços e Reembolso em sua reunião de 20-22 de abril de 2022;</li> <li>• A Resolução n.º 35, de 28 de julho de 2022, do Conselho de Administração da AIFA, adotada sob proposta do Diretor Geral, relativa à aprovação de medicamentos para de autorização de introdução no mercado e de participação pelo Serviço Nacional de Saúde. pelo Serviço Nacional de Saúde.</li> </ul>
Link	<a href="https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-09-12&amp;atto.codiceRedazionale=22A05208&amp;elenco30giorni=false">https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-09-12&amp;atto.codiceRedazionale=22A05208&amp;elenco30giorni=false</a>
AOTMiT, 2024, Polónia	
Tipo de Recomendação	Positiva
População	



<p>Justificativa</p>	<ul style="list-style-type: none"> <li>• Os resultados dos ensaios clínicos disponíveis são interpretados levando em consideração a necessidade não atendida de pacientes com acondroplasia devido à falta de opções de tratamento disponíveis</li> <li>• Os ECRs mostram um benefício nos parâmetros de crescimento, ou seja, VCA, escore Z de crescimento na população pediátrica. Ao mesmo tempo, deve-se enfatizar que há limitações fundamentais em ser capaz de tirar conclusões inequívocas (fases de extensão dos estudos - 111-208 e 111-302) sobre a eficácia a longo prazo e a persistência do efeito benéfico da vosoritida ao longo do tempo devido ao número muito pequeno/ausência de pacientes com resultados disponíveis para os parâmetros avaliados, além disso, os dados vêm dos relatórios confidenciais do Requerente.</li> <li>• Em vista da eficácia da terapia na melhoria do crescimento do paciente, um impacto positivo da intervenção do ensaio na qualidade de vida dos pacientes poderia ser potencialmente esperado. Dados da fase de extensão do estudo 111-302 para o período de acompanhamento de 3 anos podem sugerir um benefício em termos de melhor qualidade de vida (mudança na pontuação do questionário QoLISSY em relação aos valores basais) na subpopulação de pacientes que alcançaram melhora no parâmetro de crescimento, escore Z.</li> <li>• Os dados disponíveis estão sujeitos a incertezas - a necessidade de estudos adicionais para confirmar os efeitos de longo prazo do tratamento é indicada. Atualmente, não há dados clínicos disponíveis para concluir sobre o efeito do vosoritida no alívio de complicações relacionadas à acondroplasia.</li> <li>• A vosoritida é a primeira terapia medicamentosa direcionada à causa da doença a ter um perfil de segurança aceitável. Os eventos adversos mais comuns experimentados durante o uso da vosoritida incluíram reações locais relacionadas à administração do medicamento, a maioria dos EAs observados foram leves em gravidade e transitórios.</li> </ul>
<p>Link</p>	<p><a href="#">TBD</a></p>

### 9.3. ANEXO III – Estudos excluídos da revisão sistemática

**Tabela 38. Lista de estudos excluídos**

Autor	Título	Referência	DOI	Justificativa
Dauber A., McCarthy T., Zhang A., Boucher K., Merchant N., Dham N., Shankar R.K.	A Prospective Clinical Trial of Vosoritide in Selected Genetic Causes of Short Stature	Hormone Research in Paediatrics (2022) 95 Supplement 1 (137-138). Date of Publication: 1 Jul 2022	10.1159/000525242	Indicação não corresponde
Boucher K., Dham N., Shankar R.K., McCarthy T., Merchant N., Zhang A., Dauber A.	A Prospective Clinical Trial of Vosoritide in Selected Genetic Causes of Short Stature	Journal of the Endocrine Society (2022) 6 Supplement 1 (A618-A619). Date of Publication: 1 Nov 2022	10.1210/jendso/bvac150.1282	Indicação não corresponde
Savarirayan, R; Tofts, L; Irving, M; Wilcox, W; Bacino, C; Hoover-Fong, J; Font, RU; Harmatz, P; Rutsch, F; Bober, M; Polgreen, L; Ginebreda, I; Mohnike, K; Charrow, J; Hoernschmeyer, D; Ozono, K; Alanay, Y; Arundel, P; Kagami, S; Yasui, N; White, K; Saal, H; Leiva-Gea, A; Luna-Gonzalez, F; Mochizuki, H; Basel, D; Porco, D; Jayaram, K; Fischeleva, E; Huntsman-Labed, A; Day, J	A Randomized Controlled Trial of Vosoritide in Children with Achondroplasia	Journal of bone and mineral research	10.1002/jbmr.4206	Resumo de congresso
Polgreen L., Savarirayan R., Tofts L., Irving M., Wilcox W., Bacino C., Hoover-Fong J., Ullot Font R., Harmatz P., Rutsch F., Bober M., Ginebreda I., Mohnike K., Charrow J., Hoernschmeyer D., Ozono K., Alanay Y., Arundel P., Kagami S., Yasui N., White K., Saal H., Leiva-Gea A., Luna-González F., Mochizuki H., Basel D.,	A randomized controlled trial of vosoritide in children with achondroplasia	Hormone Research in Paediatrics (2020) 93:SUPPL 1 (169-170). Date of Publication: 1 Jul 2020	10.1159/000509566	Resumo de congresso



Porco D., Jayaram K., Fisheleva E., Huntsman-Labed A., Day J.				
Savarirayan, R; Tofts, L; Irving, M; Wilcox, W; Bacino, CA; Hoover-Fong, J; Ullot Font, R; Harmatz, P; Rutsch, F; Bober, MB; Polgreen, LE; Ginebreda, I; Mohnike, K; Charrow, J; Hoernschmeyer, D; Ozono, K; Alanay, Y; Arundel, P; Kagami, S; Yasui, N; White, K; Saal, HM; Leiva-Gea, A; Luna-Gonzales, F; Mochizuki, H; Basel, D; Porco, DM; Jayaram, K; Fisheleva, E; Huntsman-Labed, A; Day, J	A Randomized Controlled Trial of Vosoritide in Children With Achondroplasia	Journal of the Endocrine Society	10.1210/jendso/bvaa046.2081	Resumo de congresso
Savarirayan, R; Wilcox, WW; Harmatz, P; Phillips, J; Polgreen, LE; Tofts, L; Ozono, K; Arundel, P; Irving, M; Bacino, CA; Basel, D; Bober, MB; Charrow, J; Mochizuki, H; Kotani, Y; Saal, HM; Jeha, G; Han, L; Fisheleva, E; Huntsman-Labed, A; Day, J	A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia	Twin research and human genetics	10.1017/thg.2023.7	Resumo de congresso
Polgreen, LE; Savarirayan, R; Wilcox, WW; Harmatz, P; Phillips, J; Tofts, L; Ozono, K; Arundel, P; Irving, M; Bacino, CA; Basel, D; Bober, MB; Charrow, J; Mochizuki, H; Kotani, Y; Saal, HM; Jeha, G; Han, L; Fisheleva, E; Huntsman-Labed, A; Day, J	A randomized controlled trial of vosoritide in infants and toddlers with achondroplasia	Hormone research in paediatrics	10.1159/000529083	Resumo de congresso



Polgreen, LE; Savarirayan, R; Wilcox, WW; Harmatz, P; Phillips, J; Tofts, L; Ozono, K; Arundel, P; Irving, M; Bacino, CA; Basel, D; Bober, MB; Charrow, J; Mochizuki, H; Kotani, Y; Saal, HM; Han, L; Jeha, G; Day, J; Huntsman-Labed, A; Fischeleva, E	A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia	Hormone research in paediatrics	10.1159/000531602	Resumo de congresso
Polgreen L.E., Savarirayan R., Wilcox W.W., Harmatz P., Phillips J., Tofts L., Ozono K., Arundel P., Irving M., Bacino C.A., Basel D., Bober M.B., Charrow J., Mochizuki H., Kotani Y., Saal H.M., Han L., Jeha G., Day J., Huntsman-Labed A., Fischeleva E.	A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia	Hormone Research in Paediatrics (2023) 96 Supplement 3 (141-143). Date of Publication: 1 Aug 2023	10.1159/000531602	Resumo de congresso
Savarirayan R., Wilcox W.W., Harmatz P., Phillips J., Polgreen L.E., Tofts L., Ozono K., Arundel P., Irving M., Bacino C.A., Basel D., Bober M.B., Charrow J., Mochizuki H., Kotani Y., Saal H.M., Jeha G., Han L., Fischeleva E., Huntsman-Labed A., Day J.	A Randomized Controlled Trial Of Vosoritide In Infants And Toddlers With Achondroplasia	Journal of the Endocrine Society (2022) 6 Supplement 1 (A591-A592). Date of Publication: 1 Nov 2022	10.1210/jendso/bvac150.1225	Resumo de congresso
Wrobel W., Ben-Skowronek I.	Assessment of the efficacy of vosoritide therapy in children with achondroplasia in clinical trials	Translational Pediatrics (2024) 13:9 (1515-1516). Date of Publication: 30 Sep 2024	10.21037/tp-24-249	Comentário
Derocher C., Carter E., Jepsen K., Raggio C.	Does Vosoritide treatment affect bone strength in children with achondroplasia	JBMR Plus (2024) 8 Supplement 2 (ii278-ii279). Date of Publication: 1 Aug 2024	10.1093/jbmrpl/ziae105	Resumo de congresso



Paton DM.	Efficacy of vosoritide in the treatment of achondroplasia	Drugs Today (Barc). 2022 Sep;58(9):451-456. doi: 10.1358/dot.2022.58.9.3422313.	10.1358/dot.2022.58.9.3422313	Revisão narrativa
Prickett TCR, Espiner EA, Irving M, Bacino C, Phillips JA 3rd, Savarirayan R, Day JRS, Fischeleva E, Larimore K, Chan ML, Jeha GS.	Evidence of feedback regulation of C-type natriuretic peptide during Vosoritide therapy in Achondroplasia	Sci Rep. 2021 Dec 20;11(1):24278. doi: 10.1038/s41598-021-03593-1.	10.1038/s41598-021-03593-1	Revisão narrativa
Barreda-Bonis A.-C., de Bergua Domingo J.M., Galán-Gómez E., Guillén-Navarro E., Leiva-Gea I., Riaño-Galán I.	Expert consensus for the management of patients with achondroplasia in treatment with vosoritide	Anales de Pediatría (2024). Date of Publication: 2024	10.1016/j.anpedi.2024.09.005	Resumo de congresso
Dentry T, O'Neill J, Raj S, Gardiner K, Savarirayan R.	Exploring the family experience of children aged 2-4 years receiving daily vosoritide injections: A qualitative study	J Pediatr Nurs. 2024 Jul-Aug;77:e167-e176. doi: 10.1016/j.pedn.2024.04.007. Epub 2024 Apr 10.	10.1016/j.pedn.2024.04.007	Resumo de congresso
Jacob A., Mustafa M., Elabiary M., Mughal M.Z., Thalange N.	Growth response to Vosoritide in achondroplasia - real world experience from a tertiary centre in the UAE	JBMR Plus (2024) 8 Supplement 2 (ii340-ii341). Date of Publication: 1 Aug 2024	10.1093/jbmrpl/ziae105	Resumo de congresso
Savarirayan R, Baratela W, Butt T, Cormier-Daire V, Irving M, Miller BS, Mohnike K, Ozono K, Rosenfeld R, Selicorni A, Thompson D, White KK, Wright M, Fredwall SO.	Literature review and expert opinion on the impact of achondroplasia on medical complications and health-related quality of life and expectations for long-term impact of vosoritide: a modified Delphi study	Orphanet J Rare Dis. 2022 Jun 13;17(1):224. doi: 10.1186/s13023-022-02372-z.	10.1186/s13023-022-02372-z	Opinião de especialistas
Kunkel P., Al Halak M., Bechthold-Dalla Pozza S., Grasmann C., Keller A., Muschol N., Nader S., Palm K., Poetzsch S., Rohrer T., Rutsch F., Schnabel D., Voelkl T., Vogt B.,	Multidisciplinary approach in achondroplasia - real world experience after drug approval of vosoritide	Hormone Research in Paediatrics (2023) 96 Supplement 4 (173). Date of Publication: 1 Sep 2023	10.1159/000533803	Resumo de congresso



Wechsung K., Weigel J., Woelfle J., Pfaeffle R., Gausche R., Beger C., Mohnike K.				
NiMhurchadha S., Butler K., Argent R., Palm K., Baujat G., Cormier-Daire V., Mohnike K.	Parents' Experience of Administering Vosoritide: A Daily Injectable for Children with Achondroplasia	Advances in Therapy (2023) 40:5 (2457-2470). Date of Publication: 1 May 2023	10.1007/s12325-023-02496-z	Questionário com família
Polgreen L.E., Hoover-Fong J., Irving M., Bacino C.A., Charrow J., Cormier-Daire V., Harmatz P., Sabir I., Fischeleva E., Huntsman-Labed A., Phillips J., Savarirayan R.	Persistence of Growth Promoting Effects in Children with Achondroplasia Over Seven Years: Update from Phase II Extension Study with Vosoritide	Hormone Research in Paediatrics (2023) 96 Supplement 3 (151-152). Date of Publication: 1 Aug 2023	10.1159/000531602	Resumo de congresso
Savarirayan R., Wilcox W.R., Harmatz P., Phillips J., Irving M., Polgreen L.E., Tofts L., Ozono K., Arundel P., Bacino C., Basel D., Carroll R.S., Charrow J., Mochizuki H., Kotani Y., Saal H.M., Han L., Low A., Day J.	Persistence of growth promoting effects in infants and toddlers with achondroplasia: Results from a phase 2 extension study with Vosoritide	JBMR Plus (2024) 8 Supplement 2 (ii174-ii175). Date of Publication: 1 Aug 2024	10.1093/jbmrpl/ziae105	Resumo de congresso
Savarirayan R., Irving M., R Wilcox W., Harmatz P., Phillips J., Polgreen L.E., Tofts L., Ozono K., Arundel P., Bacino C.A., Basel D., Bober M.B., Charrow J., Mochizuki H., Kotani Y., Saal H.M., Han L., Sabir I., Fischeleva E., Huntsman-Labed A., Day J.	Persistence of Growth Promoting Effects in Infants and Toddlers with Achondroplasia: Results in Children Aged Over 2 Years Old from a Phase II Extension Study with Vosoritide	Hormone Research in Paediatrics (2023) 96 Supplement 4 (41-42). Date of Publication: 1 Sep 2023	10.1159/000533803	Resumo de congresso
Savarirayan, R; Tofts, L; Irving, M; Wilcox, W; Bacino, CA; Hoover-Fong, J; Font, RU; Harmatz, P; Rutsch, F; Bober, MB; Polgreen, L; Ginebreda, I; Mohnike, K; Charrow,	Persistent and Stable Growth Promoting Effects of Vosoritide in Children With Achondroplasia for up to 2 Years: results From the Ongoing	Journal of the Endocrine Society	10.1210/jendso/bvab048.1368	Resumo de congresso



<p>J; Hoernschemeyer, D; Ozono, K; Alanay, Y; Arundel, P; Kagami, S; Yasui, N; White, K; Saal, H; Leiva-Gea, A; Luna-Gonzalez, F; Mochizuki, H; Basel, D; Porco, D; Jayaram, K; Fischeleva, E; Han, L; Day, J</p>	<p>Phase 3 Extension Study</p>			
<p>Polgreen, LE; Savairayan, R; Tofts, L; Irving, M; Wilcox, W; Bacino, CA; Hoover-Fong, J; Font, RUFU; Harmatz, P; Rutsch, F; Bober, MB; Ginebreda, I; Mohnike, K; Charrow, J; Hoernschemeyer, D; Ozono, K; Alanay, Y; Arundel, P; Kagami, S; Yasui, N; White, K; Saal, HM; Leiva-Gea, A; Luna-Gonzalez, F; Mochizuki, H; Basel, D; Porco, DM; Jayaram, K; Fischeleva, E; Lawrinson, S; Day, J</p>	<p>Persistent and stable growth promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: results from an ongoing Phase 3 extension study</p>	<p>Hormone research in paediatrics</p>	<p>10.1159/000529083</p>	<p>Resumo de congresso</p>
<p>Savairayan, R; Tofts, L; Irving, M; Wilcox, W; Bacino, CA; Hoover-Fong, J; Font, RU; Harmatz, P; Rutsch, F; Bober, MB; Polgreen, LE; Ginebreda, I; Mohnike, K; Charrow, J; Hoernschemeyer, D; Ozono, K; AlanayD, Y; Arundel, P; Kagami, S; Yasui, N; White, K; Saal, HM; Leiva-Gea, A; Luna-Gonzalez, F; Mochizuki, H; Basel, D; Porco, DM; Jayaram, K; Fischeleva, E; Han, L; Day, J</p>	<p>Persistent growth in children with achondroplasia treated with vosoritide for two years: further evidence supporting the first precision therapy for this condition</p>	<p>Twin research and human genetics</p>	<p>10.1017/thg.2021.44</p>	<p>Resumo de congresso</p>



<p>Savarirayan R, Irving M, Wilcox WR, Bacino CA, Hoover-Fong JE, Harmatz P, Polgreen LE, Mohnike K, Prada CE, Kubota T, Arundel P, Leiva-Gea A, Rowell R, Low A, Sabir I, Huntsman-Labed A, Day J.</p>	<p>Persistent growth-promoting effects of vosoritide in children with achondroplasia are accompanied by improvements in physical and social aspects of health-related quality of life</p>	<p>Genet Med. 2024 Sep 18;26(12):101274. doi: 10.1016/j.gim.2024.101274. Online ahead of print.</p>	<p>10.1016/j.gim.2024.101274</p>	<p>Resumo de congresso</p>
<p>Polgreen, LE; Savarirayan, R; Tofts, L; Irving, M; Wilcox, WW; Bacino, CA; Hoover-Fong, J; Font, RU; Harmatz, P; Rutsch, F; Bober, MB; Ginebreda, I; Mohnike, K; Charrow, J; Hoernschemeyer, D; Ozono, K; Alanay, Y; Arundel, P; Yasui, N; Kagami, S; White, K; Saal, HM; Leiva-Gea, A; Luna-Gonzalez, F; Mochizuki, HM; Basel, D; Jayaram, K; Porco, DM; Day, J; Lawrinson, S; Fischeleva, E</p>	<p>Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: update from Phase 3 extension study</p>	<p>Hormone research in paediatrics</p>	<p>10.1159/000531602</p>	<p>Resumo de congresso</p>
<p>Polgreen L.E., Savarirayan R., Tofts L., Irving M., Wilcox W.W., Bacino C.A., Hoover-Fong J., Font R.U., Harmatz P., Rutsch F., Bober M.B., Ginebreda I., Mohnike K., Charrow J., Hoernschemeyer D., Ozono K., Alanay Y., Arundel P., Yasui N., Kagami S., White K., Saal H.M., Leiva-Gea A., Luna-González F., Mochizuki H.M., Basel D., Jayaram K., Porco D.M., Day J., Lawrinson S., Fischeleva E.</p>	<p>Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: update from Phase 3 extension study</p>	<p>Hormone Research in Paediatrics (2023) 96 Supplement 3 (149-151). Date of Publication: 1 Aug 2023</p>	<p>10.1159/000531602</p>	<p>Resumo de congresso</p>



<p>Savarirayan R., Tofts L., Irving M., Wilcox W.R., Bacino C.A., Hoover-Fong J.E., Harmatz P., Rutsch F., Carroll R.S., Polgreen L.E., Mohnike K., Charrow J., Prada C., Hoernschemeyer D., Ozono K., Kubota T., Alanay Y., Arundel P., Kotani Y., Yasui N., White K.K., Brandstetter S., Saal H.M., Leiva-Gea A., Mochizuki H., Tajima A., Basel D., Fischeleva E., Low A., Lawrinson S., Day J.</p>	<p>Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 4 years: Update from phase 3 extension study</p>	<p>JBMR Plus (2024) 8 Supplement 2 (ii176-ii177). Date of Publication: 1 Aug 2024</p>	<p>10.1093/jbmrpl/ziae105</p>	<p>Resumo de congresso</p>
<p>Savarirayan R., Tofts L., Irving M., Wilcox W.R., Bacino C.A., Hoover-Fong J.E., Harmatz P., Rutsch F., Carroll R.S., Polgreen L.E., Mohnike K., Charrow J., Prada C., Hoernschemeyer D., Ozono K., Kubota T., Alanay Y., Arundel P., Kotani Y., Yasui N., White K.K., Brandstetter S., Saal H.M., Leiva-Gea A., Mochizuki H., Tajima A., Basel D., Fischeleva E., Rowell R., Huntsman-Labed A., Day J.</p>	<p>Persistent growth-promoting effects of vosoritide in children with achondroplasia is accompanied by improvement in physical aspects of quality of life</p>	<p>JBMR Plus (2024) 8 Supplement 2 (ii37-ii38). Date of Publication: 1 Aug 2024</p>	<p>10.1093/jbmrpl/ziae105</p>	<p>Resumo de congresso</p>
<p>Chan ML, Qi Y, Larimore K, Cherukuri A, Seid L, Jayaram K, Jeha G, Fischeleva E, Day J, Huntsman-Labed A, Savarirayan R, Irving M, Bacino CA, Hoover-Fong J, Ozono K, Mohnike K, Wilcox WR, Horton WA, Henshaw J.</p>	<p>Pharmacokinetics and Exposure-Response of Vosoritide in Children with Achondroplasia</p>	<p>Clin Pharmacokinet. 2022 Feb;61(2):263-280. doi: 10.1007/s40262-021-01059-1. Epub 2021 Aug 25.</p>	<p>10.1007/s40262-021-01059-1</p>	<p>Farmacocinética</p>



Galetaki D, Zhang A, Qi Y, Merchant N, Kanakatti Shankar R, Boucher K, Shafaei N, Seaforth R, Dham N, Dauber A.	Phase 2 Trial of Vosoritide Use in Patients with Hypochondroplasia: A Pharmacokinetic/ Pharmacodynamic Analysis	Horm Res Paediatr. 2024 Oct 18:1-16. doi: 10.1159/000542102. Online ahead of print.	10.1159/000542102	Farmacocinética
Savarirayan, R; Irving, M; Maixner, W; Thompson, D; Offiah, AC; Connolly, DJ; Raghavan, A; Powell, J; Kronhardt, M; Jeha, G; Ghani, S; Fischeleva, E; Day, JR	Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery	Science progress	10.1177/00368504211003782	Desenho do estudo
Palm K., Pozza S.B.-D., Gausche R., Högler W., Hoyer-Kuhn H., Hübner A., Keller A., Mirante A., Mohnike K., Muschol N., Nader S., Pfäffle R., QUITTER F., Rohrer T., Rutsch F., Schnabel D., Semler O., Silva I., Sousa S.B., Voelkl T.M.K., Wechsung K., Weigel J., Woelffle J., Lausch E.	Real-world data in children with achondroplasia after licensing of Vosoritide	Hormone Research in Paediatrics (2022) 95 Supplement 2 (151). Date of Publication: 1 Sep 2022	10.1159/000525606	Resumo de congresso
Cormier-Daire V., Cohen S., Edouard T., Isidor B., Mukherjee S., Pimenta J., Rossi M., Schaefer E., Sigaudy S., Baujat G.	Real-world experience with Vosoritide for achondroplasia: interim findings from an early access programme in France	Hormone Research in Paediatrics (2022) 95 Supplement 2 (308-309). Date of Publication: 1 Sep 2022	10.1159/000525606	Resumo de congresso
Cormier-Daire V., Edouard T., Isidor B., Cohen S., Mukherjee S., Pimenta J., Lhaneche L., Rossi M., Schaefer E., Goodman E., Sigaudy S., Baujat G.	Real-world safety and effectiveness of vosoritide: Results from an early access program in France	Hormone Research in Paediatrics (2023) 96 Supplement 4 (90). Date of Publication: 1 Sep 2023	10.1159/000533803	Resumo de congresso



Al Shouli R., Elnaem B., Farooq A.	SAFETY AND EFFICACY OF VOSORITIDE IN PATIENTS WITH ACHONDROPLASIA- A SYSTEMATIC REVIEW	Archives of Disease in Childhood (2024) 109 Supplement 1 (A230). Date of Publication: 1 Aug 2024	10.1136/archdischild-2024-rcpch.356	Resumo de congresso
Nishioka A, Adachi N, Tanaka H, Oda Y.	Two Cases of Cardiovascular Adverse Events Following Subcutaneous Vosoritide Injection in Early Infancy	Cureus. 2024 May 5;16(5):e59695. doi: 10.7759/cureus.59695. eCollection 2024 May.	10.7759/cureus.59695	Série de caso
Irving M., Bacino C., Cao X., Charrow J., Cormier-Daire V., Harmatz P., Katz L., Phillips J., Vaidya S., Hoover-Fong J., Savarirayan R.	Vosoritide (BMN 111) in children with achondroplasia: Results from a phase 2, open-label, sequential cohort, doseescalation study	Journal of Bone and Mineral Research (2015) 30 Supplement 1. Date of Publication: 1 Feb 2015	10.1002/jbmr.2763	Resumo de congresso
Larimore K., Nguyen T., Qi Y., Jeha G., Zoog S.	Vosoritide clinical study data demonstrates CXM is a superior biomarker of endochondral bone growth	Hormone Research in Paediatrics (2021) 94:SUPPL 1 (211). Date of Publication: 2021	10.1159/000518849	Avaliação de biomarcador
Irving M., Hoover-Fong J., Bacino C., Charrow J., Cormier-Daire V., Dickson P., Harmatz P., Labed A.H., Jayaram K., Jeha G., Day J., Larimore K., Phillips J., Savarirayan R.	Vosoritide for children with achondroplasia: A 30 month update from an ongoing phase 2 clinical trial	Hormone Research in Paediatrics (2018) 90 Supplement 1 (76). Date of Publication: 1 Sep 2018	10.1159/000492307	Resumo de congresso
Polgreen L.E., Irving M., Hoover-Fong J., Bacino C., Charrow J., Cormier-Daire V., Dickson P., Harmatz P., Larimore K., Jayaram K., Labed A.H., Fischeleva E., Jeha G., Day J., Phillips J., Savarirayan R.	Vosoritide for children with achondroplasia: A 60-month update from an ongoing phase 2 clinical trial	Hormone Research in Paediatrics (2021) 94:SUPPL 2 (134). Date of Publication: 1 Sep 2021		Resumo de congresso
Hoover-Fong J., Irving M., Bacino C., Charrow	Vosoritide for children with achondroplasia: a	Molecular Genetics and Metabolism (2021)	10.1016/S1096-7192(21)00236-5	Resumo de congresso



J., Cormier-Daire V., Polgreen L., Dickson P., Harmatz P., Larimore K., Jayaram K., Labeled A.H., Fischeleva E., Jeha G., Day J., Phillips J., Savarirayan R.	60-month update from an ongoing phase 2 clinical trial	132 Supplement 1 (S101). Date of Publication: 1 Apr 2021		
Polgreen L.E., Irving M., Hoover-Fong J., Bacino C.A., Charrow J., Cormier-Daire V., Harmatz P., Dickson P., Bober M.B., Mohnike K., Wilcox W.R., Huntsman Labeled A., Lawrinson S., Fischeleva E., Jeha G., Day J., Phillips J., Savarirayan R.	Vosoritide for Children with Achondroplasia: Growth Velocity and Pubertal Milestones	Hormone Research in Paediatrics (2022) 95 Supplement 1 (138-140). Date of Publication: 1 Jul 2022	10.1159/000525242	Resumo de congresso
Semler O., Cormier-Daire V., Lausch E., Bober M.B., Carroll R., Sousa S.B., Deyle D., Faden M., Hartmann G., Huser A.J., Legare J.M., Mohnike K., Rohrer T.R., Rutsch F., Smith P., Travessa A.M., Verardo A., White K.K., Wilcox W.R., Hoover-Fong J.	Vosoritide Therapy in Children with Achondroplasia: Early Experience and Practical Considerations for Clinical Practice	Advances in Therapy (2024) 41:1 (198-214). Date of Publication: 1 Jan 2024	10.1007/s12325-023-02705-9	Opinião de especialistas
Allegri A.E.M., Tedesco C., Di Iorgi N., Napoli F., Fava D., Angelelli A., Casalini E., Pistorio A., Maghnie M.	Vosoritide therapy in children with achondroplasia: Early experience in an Italian cohort	JBMR Plus (2024) 8 Supplement 2 (ii189-ii190). Date of Publication: 1 Aug 2024	10.1093/jbmrpl/ziae105	Resumo de congresso
Verardo A., Semler O., Cormier-Daire V., Lausch E., Carroll R., Bober M.B., Sousa S.B., Deyle D., Faden M., Hartmann G., Huser A., Legare J., Mohnike K., Rohrer T., Rutsch F., Smith P., Travessa A., White K., Wilcox W.W., Hoover-Fong J.	Vosoritide Therapy in Patients with Achondroplasia: Early Experience and Practical Considerations for Clinical Practice	Hormone Research in Paediatrics (2023) 96 Supplement 3 (152-154). Date of Publication: 1 Aug 2023	10.1159/000531602	Resumo de congresso



<p>Simran, S KDS, Dushantrao SC, Joga R, Kumar S.</p>	<p>Vosoritide, a miracle drug, covering unmet need in achondroplasia: A regulatory update</p>	<p>Intractable Rare Dis Res. 2023 Nov;12(4):257-261. doi: 10.5582/irdr.2023.010 55.</p>	<p>10.5582/irdr.2023.010 55</p>	<p>Revisão narrativa</p>
<p>Desch M.</p>	<p>Vosoritide: A C-type natriuretic peptide analog for the therapy of achondroplasia</p>	<p>Arzneimitteltherapie (2021) 39:10 (352-353). Date of Publication: 1 Oct 2021</p>	<p>Revisão narrativa</p>	

## 9.4. ANEXO IV – Detalhamento do desenho dos estudos clínicos

### 9.2.1. Estudo 301

#### Características do estudo

O estudo principal 111-301 é um estudo multicêntrico de Fase III, randomizado, controlado por placebo e duplo-cego. Esse estudo de 60 semanas (até 4 semanas de triagem, 52 semanas de tratamento com mais 4 semanas de acompanhamento de segurança) permite a avaliação do efeito da administração diária de vosoritida na velocidade de crescimento anualizada (VCA), no crescimento (escore Z de altura) e nas proporções corporais (razão entre os segmentos superior e inferior do corpo) em indivíduos tratados com vosoritida em comparação com o grupo placebo, bem como a caracterização adicional de sua segurança e tolerabilidade em crianças com HAC. O estudo também avaliou a QoL e a função diária dos indivíduos por meio de avaliações da QoL relacionada à saúde (HRQoL) e da independência funcional. A eficácia em longo prazo e outros pontos finais continuam a ser acompanhados em indivíduos que continuam no estudo de extensão após terem concluído o período de tratamento de 52 semanas no 111-301[149].

#### Análises

##### Cálculo de potência

Com 55 pacientes planejados em cada um dos dois grupos randomizados, o poder de detectar uma diferença de 1,75 cm/ano entre o grupo vosoritida e o grupo placebo na alteração da linha de base na velocidade de crescimento anualizada em 12 meses foi de aproximadamente 90%. Isso pressupõe que o DP combinado da alteração da linha de base na velocidade de crescimento anualizada foi de 2,80 cm/ano, usando um teste *t bilateral* de duas amostras com nível de significância de 0,05. O cálculo do poder foi baseado nos dados do Estudo 111-202 [150]. Todas as análises foram feitas com o SAS versão 9.4, usando o procedimento Proc MIXED [108].

##### *Análises estatísticas*



A taxa de erro geral do tipo I para testar os desfechos de eficácia primários e secundários principais usando um modelo de análise de covariância (ANCOVA) foi controlada no nível de significância bilateral de 0,05 usando um procedimento de comparações múltiplas de gatekeeping em série de três etapas. Seguindo esse procedimento de comparações múltiplas, o avanço para a próxima etapa só ocorria se as hipóteses nulas em uma etapa e na(s) etapa(s) anterior(es) fossem todas rejeitadas ao nível de significância de 0,05 a favor da vosoritida. Se qualquer hipótese nula em uma etapa não fosse rejeitada ou fosse rejeitada, mas não a favor da vosoritida, os testes de hipótese correspondentes a todas as etapas subsequentes não seriam considerados confirmatórios. Todos os testes de hipótese foram bilaterais. Os modelos que testaram a diferença de tratamento sempre incluíram as seguintes covariáveis de linha de base: estratos (estágio I de Tanner masculino, estágio I de Tanner feminino, estágio >I de Tanner masculino, estágio >I de Tanner feminino); idade, velocidade de crescimento anualizada e escore Z de altura [108].

Um procedimento de imputação múltipla, PROC MI, deveria ser usado para a análise do desfecho primário a fim de contabilizar os dados ausentes. Entretanto, se não houvesse dados suficientes para aplicar esse procedimento, seria usada uma abordagem alternativa pré-especificada, aplicando a velocidade de crescimento anualizada da linha de base à última avaliação de altura disponível. Como havia apenas dois pacientes com dados faltantes, essa abordagem de imputação foi usada para a análise do desfecho primário. Os dois pacientes no braço de tratamento com vosoritida sem uma avaliação da altura em pé na semana 52 tiveram sua altura em pé faltante na semana 52 imputada pela aplicação da velocidade de crescimento anualizada da linha de base à última avaliação de altura disponível. Posteriormente, esses valores de altura em pé imputados foram usados para calcular a velocidade de crescimento anualizada e o escore Z de altura na Semana 52 [108].

Seis análises de subgrupo pré-especificadas também foram realizadas em cada um dos desfechos primários e dois desfechos secundários importantes de eficácia. Os gráficos de floresta fornecem um resumo geral para os desfechos primários e secundários principais e de cada subgrupo, mostrando a diferença entre a alteração média dos quadrados mínimos do grupo de tratamento em relação à linha de base e o IC de 95% para a diferença, na Semana 52.

#### *Análises de segurança*



Todos os pacientes randomizados e consentidos, constituindo o conjunto completo de análise, foram incluídos de acordo com os princípios de intenção de tratar para as análises de eficácia (n=121). Todos os pacientes que receberam pelo menos uma dose de vosoritida ou placebo (n=121) foram incluídos nas análises de segurança. A população de segurança foi definida como todos os pacientes no conjunto completo de análise que receberam pelo menos uma dose de vosoritida ou placebo. A segurança foi avaliada examinando-se a incidência, a gravidade e a relação com o medicamento em estudo de todos os eventos adversos emergentes do tratamento relatados durante o período do estudo. Além disso, foram avaliadas as alterações em relação à linha de base nos resultados laboratoriais clínicos e nos sinais vitais. As tabelas de resumo por grupo de tratamento incluíram todos os eventos de segurança até 30 dias após a interrupção do tratamento [108].

#### *Velocidade de crescimento anualizada (VCA)*

A velocidade de crescimento anualizada da linha de base foi calculada a partir da altura em pé medida nos últimos 6 meses do estudo de execução. A velocidade de crescimento anualizada pós-baseline foi calculada a partir da altura em pé em 52 semanas e, em seguida, resumida por grupo de tratamento. A alteração da linha de base na velocidade de crescimento anualizada foi derivada para cada paciente como a diferença entre a velocidade de crescimento anualizada pós-linha de base e a linha de base. Os dados individuais dos 121 pacientes randomizados foram então avaliados no modelo ANCOVA. A altura em pé foi convertida em um escore Z adequado à idade e ao sexo por comparação com os padrões de referência do CDC.

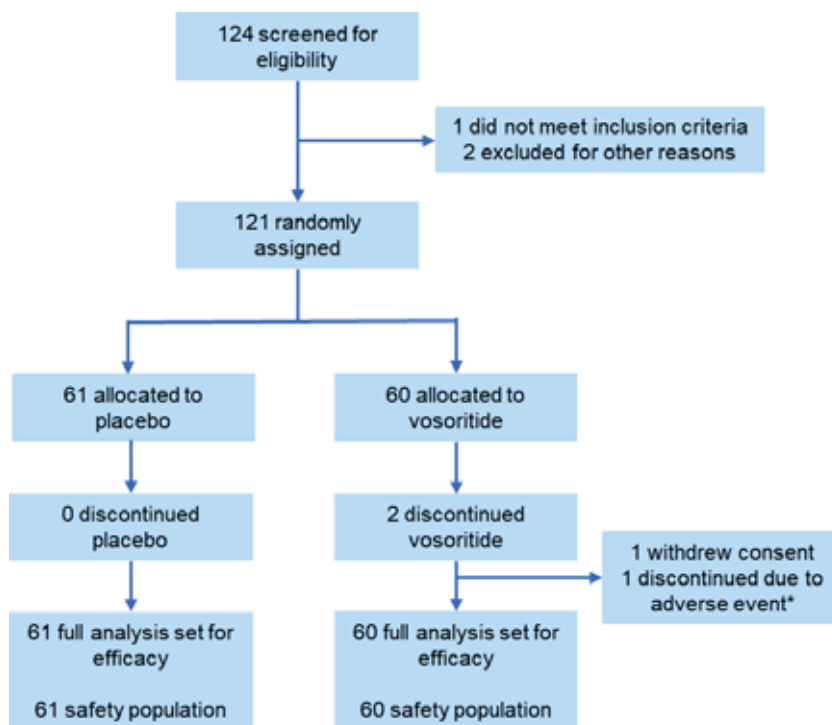
#### *Proporção de segmentos da parte superior e inferior do corpo*

A razão entre os segmentos superior e inferior do corpo foi calculada como a razão entre a altura sentada e a altura em pé menos a altura sentada.

#### **População e disposição dos pacientes**

A disposição dos pacientes em 111-301 é apresentada na Figura 43. Um total de 121 pacientes foi incluído no estudo; 61 pacientes foram randomizados para receber placebo e 60 pacientes para receber vosoritida 15 µg/kg. Dois pacientes do grupo do vosoritida foram descontinuados durante o estudo [149].

**Figura 43. Disposição do paciente para 111-301 (conjunto completo de análise)**



\*Ansiedade por injeção.  
 Fonte: Savarirayan et. al, [41]

**Dados demográficos e características de linha de base**

Um resumo das características de linha de base para o conjunto completo de análise (FAS) é apresentado na Tabela 39. No grupo placebo, a idade média (DP) no Dia 1 foi de 9,06 (2,47) anos (idade média de 9,31 anos) e foi ligeiramente menor no grupo vosoritida (8,35 [2,43] anos, idade média de 7,78 anos). Houve uma distribuição semelhante de pacientes do sexo masculino e feminino nos dois grupos de tratamento.

**Tabela 39. Dados demográficos e características da doença na linha de base do estudo 111-301**

Variável	Placebo (n=61)	Vosoritida 15µg/kg (n=60)	Geral (n=121)
Idade no Dia 1 anos,	9.06 (2.47)	8.35 (2.43)	8.71 (2.47)

<b>média (DP)</b>			
<b>Idade no Dia 1, n (%)*</b>			
<b>≥ 5 a &lt; 8 anos</b>	24 (39.3)	31 (51.7)	55 (45.5)
<b>≥ 8 a &lt; 11 anos</b>	24 (39.3)	17 (28.3)	41 (33.9)
<b>≥ 11 a &lt; 15 anos</b>	13 (21.3)	12 (20.0)	25 (20.7)
<b>Sexo, n (%)*</b>			
<b>Masculino</b>	33 (54.1)	31 (51.7)	64 (52.9)
<b>Feminino</b>	28 (45.9)	29 (48.3)	57 (47.1)
<b>Raça, n (%)*</b>			
<b>Branco</b>	41 (67.2)	45 (75.0)	86 (71.1)
<b>Asiático</b>	13 (21.3)	10 (16.7)	23 (19.0)
<b>Outros</b>	9 (14.8)	7 (11.7)	16 (13.2)
<b>Japonês</b>	4 (6.6)	3 (5.0)	7 (5.8)
<b>Múltiplos</b>	5 (8.2)	2 (3.3)	7 (5.8)
<b>Negro de afro-americano</b>	2 (3.3)	3 (5.0)	5 (4.1)
<b>Etnia, n (%)*</b>	55 (90.2)	59 (98.3)	114 (94.2)

Não hispânico ou latino	6 (9.8)	1 (1.7)	7 (5.8)
Hispânico ou latino			
<b>Estágio de Tanner , n (%)**</b>			
I	48 (78.7)	48 (80.0)	96 (79.3)
>II	13 (21.3)	12 (20.0)	25 (20.7)
<b>Peso, kg, média (DP)</b>	24.62 (9.07)	22.88 (7.96)	23.76 (8.55)
<b>Escore Z de peso, média (DP)</b>	-1.62 (1.44)	-1.49 (1.19)	-1.56 (1.32)
<b>IMC, kg/m<sup>2</sup>, média (DP)</b>	22.64 (5.43)	22.22 (3.44)	22.43 (4.54)
<b>Escore Z do IMC, média (DP) (n)</b>	1.71 (0.61)	1.86 (0.62)	1.78 (0.61)

IMC, índice de massa corporal; Máx, máximo; Mín, mínimo; DP, desvio padrão.

\* As porcentagens foram calculadas usando o número total de indivíduos no conjunto completo de análise (N para cada grupo de tratamento) como denominador.

\*\*O estágio de Tanner (I, > I) é determinado usando a genitália e o estágio de Tanner da mama para homens e mulheres, respectivamente.

Os escores Z foram derivados usando dados de referência específicos de idade e sexo (médias e DP) para crianças de estatura média de acordo com os Centros de Controle e Prevenção de Doenças.

Fonte: Relatório final do estudo clínico BioMarin 111-301, 2020 [108]

## 9.2.2. Estudo 302

### *Análises*

O Relatório de Atualização de Eficácia mais recente (data de corte de dados de 25 de fevereiro de 2022) apresenta a alteração da linha de base em VCA, escore Z de altura



(referência de estatura média), escore Z de altura (referência de ACH), altura em pé e proporção entre a parte superior e inferior do corpo até a data de corte de dados . [122, 151]

A avaliação da eficácia ao longo do tempo foi avaliada na população do Full Analysis Set (FAS). O FAS foi definido de acordo com o princípio de intenção de tratar e incluiu todos os indivíduos registrados com um consentimento informado assinado em para 111-302. O FAS foi usado para apresentar as características de linha de base e os dados de eficácia.

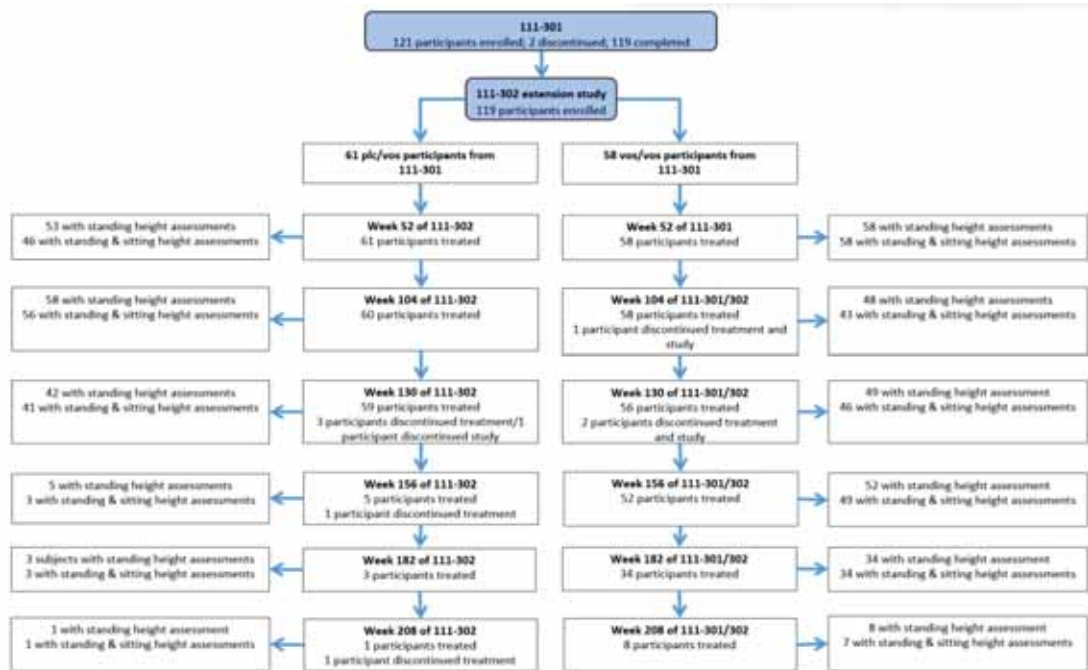
População de segurança: todos os pacientes no FAS que receberam pelo menos uma dose de vosoritida no Estudo 111-302.

Não foram realizados cálculos formais do tamanho da amostra. O tamanho da amostra neste estudo é baseado nos pacientes que concluíram o Estudo 111-301. Todos os desfechos de eficácia foram resumidos nas visitas programadas usando estatísticas descritivas. Para resumos descritivos, os dados ausentes não foram imputados.

### ***População e disposição dos pacientes***

A disposição dos pacientes no 111-302 é apresentada em [Figura 44.](#) Um total de 119 pacientes foram incluídos no 111-302, tendo concluído o estudo principal 111-301. Um total de 8 participantes interromperam o tratamento (4 dos quais também interromperam o estudo).

Figura 44. Disposição do paciente



Vos/vos, grupo vosoritida 111-301; plc/vos, grupo placebo.

As visitas são as visitas planejadas pelo CRF. As avaliações de altura foram baseadas nas visitas da janela de análise.

Fonte: Relatório de Atualização de Eficácia da BioMarin 111-302, 2023 [122]

### Dados demográficos e de linha de base

A linha de base é definida como a última avaliação antes da primeira dose de vosoritida. Para todos os dados aqui descritos, a linha de base para os indivíduos vos/vos é a mesma do estudo 111-301. A linha de base para os indivíduos plc/vos é imediatamente anterior à primeira dose de vosoritida em 111-302. Os dados demográficos de linha de base e as medidas de crescimento dos participantes registrados são fornecidos na Tabela 40.

**Tabela 40. Dados demográficos da linha de base e medidas de crescimento da linha de base no Dia 1 do medicamento ativo do estudo - Conjunto de Análise completo no estudo 111-302**

Variável	Placebo/Vosoritida (n=61)	Vosoritida/Vosoritida 15µg/kg (n=58)	Geral (n=119)
<b>Idade no Dia 1 anos, média (DP)</b>	10.07 (2.48)	8.26 (2.42)	9.18 (2.60)
<b>Idade no Dia 1, n (%)*</b>			
<b>≥ 5 a &lt; 8 anos</b>	15 (24.6)	31 (53.4) 46 (38.7)	46 (38.7)
<b>≥ 8 a &lt; 11 anos</b>	21 (34.4)	16 (27.6)	37 (31.1)
<b>≥ 11 a &lt; 15 anos</b>	24 (39.3)	11 (19.0)	35 (29.4)
<b>≥ 15 a &lt; 18 anos</b>	1 (1.6)	0	1 (0.8)
<b>Sexo, n (%)†</b>			
<b>Masculino</b>	33 (54.1)	30 (51.7)	63 (52.9)
<b>Feminino</b>	28 (45.9)	28 (48.3)	56 (47.1)
<b>Raça, n (%)*</b>			
<b>Branco</b>	41 (67.2)	44 (75.9)	85 (71.4)
<b>Asiático</b>	12 (19.7)	9 (15.5)	21 (17.6)
<b>Outros</b>	8 (13.1)	7 (12.1)	15 (12.6)

<b>Japonês</b>	4 (6.6)	2 (3.4)	6 (5.0)
<b>Múltiplos</b>	6 (9.8)	2 (3.4)	8 (6.7)
<b>Negro de afro-americano</b>	2 (3.3) 3 (5.2) 5 (4.2)	3 (5.2)	5 (4.2)
<b>Etnia, n (%)</b>			
<b>Não hispânico ou latino</b>	54 (88.5)	57 (98.3)	111 (93.3)
<b>Hispânico ou latino</b>	7 (11.5)	1 (1.7)	8 (6.7)
<b>Estágio de Tanner , n (%)**</b>			
<b>I</b>	42 (68.9)	47 (81.0)	89 (74.8)
<b>&gt;II</b>	18 (29.5)	11 (19.0)	29 (24.4)
<b>Não feito</b>	1 (1.6)	0	1 (0.8)
<b>Peso, kg, média (DP)</b>	27.53 (9.92)	22.73 (8.02)	25.19 (9.32)
<b>Escore Z de peso, média (DP)</b>	-1.59 (1.51)	-1.48 (1.17)	-1.54 (1.35)
<b>IMC, kg/m<sup>2</sup>, média (DP)</b>	23.52 (5.90)	22.09 (3.29)	22.82 (4.84)
<b>Escore Z do IMC, média</b>	1.65 (0.58)	1.86 (0.61)	1.75 (0.60)



(DP) (n)			
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IMC, índice de massa corporal; Máx, máximo; Mín, mínimo; DP, desvio padrão.

\* As porcentagens foram calculadas usando o número total de indivíduos no conjunto completo de análise (N para cada grupo de tratamento) como denominador.

\*\*O estágio de Tanner (I, > I) é determinado usando a genitália e o estágio de Tanner da mama para homens e mulheres, respectivamente.

Os escores Z foram derivados usando dados de referência específicos de idade e sexo (médias e DP) para crianças de estatura média de acordo com os Centros de Controle e Prevenção de Doenças.

Fonte: Relatório de Estudo Clínico BioMarin 111-302, 2020 [149]

## **Resultados - Resultados de eficácia**

Até a data limite de 25 de fevereiro de 2023, 52 pacientes no braço de tratamento vos/vos haviam completado 156 semanas no estudo de extensão 111-302 (recebendo 15 µg/kg de vosoritida por 208 semanas no total) e 59 pacientes no braço de tratamento plc/vos haviam completado 130 semanas no 111-302 (recebendo 15 µg/kg de vosoritida por 130 semanas no total) .[122]

### **9.2.3. Estudo 206**

#### **Análise estatística**

##### *Determinação do tamanho da amostra*

Não foram realizados cálculos formais do tamanho da amostra. Aproximadamente 70 pacientes com idade entre 0 e <60 meses no início do estudo foram planejados para participar e esse tamanho de amostra foi considerado apropriado para avaliar a eficácia e a segurança do vosoritida na população-alvo.

##### *Populações de análise*

A FAS foi definida de acordo com o princípio de intenção de tratar e incluiu todos os pacientes sentinelas e randomizados inscritos.

A FAS (randomizada) foi um subconjunto da FAS e foi considerada a população da análise primária para a avaliação dos parâmetros de eficácia do escore Z de altura, altura, VCA e razão entre os segmentos superior e inferior do corpo.

Todas as análises de segurança foram baseadas na população de segurança, que inclui todos os pacientes sentinelas e randomizados no FAS que receberam pelo menos uma dose de vosoritida ou placebo nesse estudo .[152]

##### *Ajustes para covariáveis*



As análises de eficácia usaram um modelo ANCOVA incluindo ajustes para as seguintes covariáveis de linha de base: estrato de idade da randomização, idade na linha de base, VCA de linha de base e sexo. As análises de escore Z de altura, altura em pé e proporção entre a parte superior e inferior do corpo incluíram a linha de base como uma covariável adicional . [152]

#### *Tratamento de desistências ou dados ausentes*

Para resumos descritivos, os dados ausentes não foram imputados. Para as análises baseadas em modelos, se a avaliação necessária na Semana 52 estivesse faltando, mas houvesse avaliações antes e depois da Semana 52, seria usada uma interpolação linear usando as medições mais próximas das medições antes e depois da Semana 52. Caso contrário, para aqueles sem avaliação após a Semana 52, a imputação múltipla usando dados de placebo de pacientes na mesma coorte foi usada para imputar os valores ausentes para altura e razão entre o segmento superior e inferior do corpo na Semana 52. Com exceção das datas parciais/ausentes, não houve imputação para os dados de segurança .[152]

#### *Exame de subgrupos*

As análises baseadas em modelos na população FAS foram conduzidas por coorte, e as tabelas de resumo foram apresentadas por idade estratificada na Coorte 1 ( $\geq 24$  meses a  $< 36$  meses e  $\geq 36$  meses a  $< 60$  meses) e na Coorte 2 ( $\geq 6$  meses a  $< 15$  meses e  $\geq 15$  meses a  $< 24$  meses) .[152]

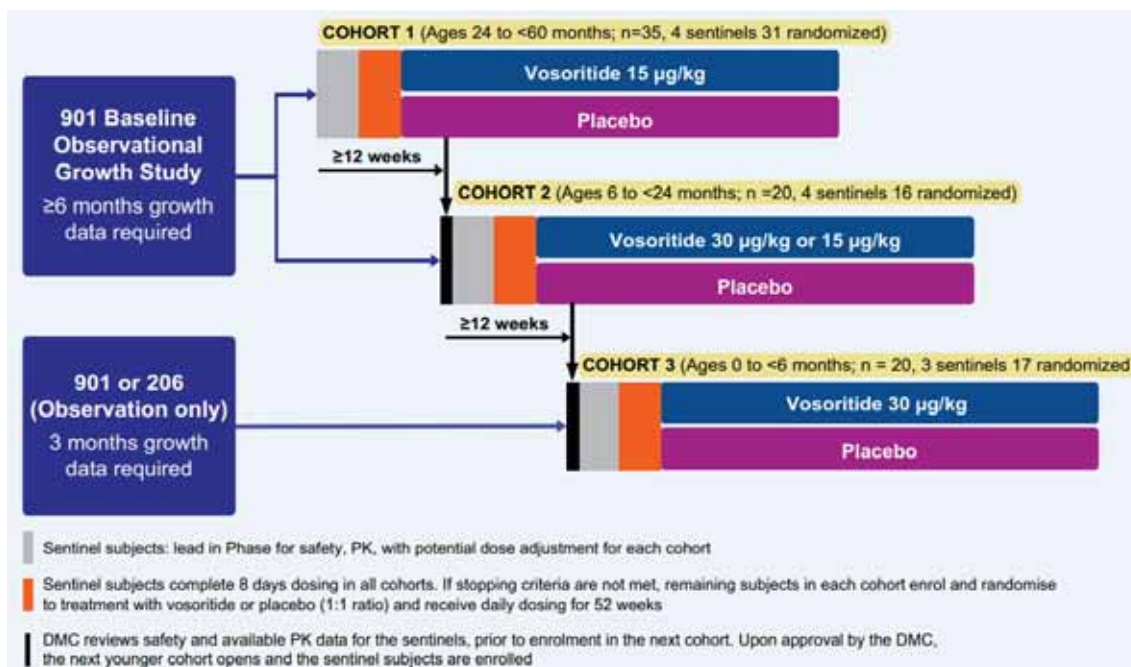
#### ***População e disposição dos pacientes***

A disposição dos pacientes no estudo 111-206 é apresentada em



Figura 45. Um total de 75 participantes (conjunto completo de análise [FAS]) foi incluído no estudo, dos quais 64 participantes foram randomizados para receber vosoritida ou placebo, o que constituiu o FAS (randomizado) e foi considerado a população de análise primária para a avaliação da eficácia, e 11 participantes foram inscritos para receber vosoritida (participantes sentinela)[152]

Figura 45. Desenho do estudo e disposição dos pacientes do 111-206



Observação: O tratamento de pacientes das coortes 2 e 3 está fora da indicação atualmente licenciada e, portanto, fora do escopo desta apresentação

Fonte: Pôster apresentado na Reunião Anual de 2022 da Endocrine Society, de 11 a 14 de junho de 2022, Atlanta, GA, Savarirayan 2022 [132]

**Dados demográficos e características de linha de base**

As características demográficas e clínicas dos pacientes na linha de base são apresentadas na Tabela 41. Em geral, os dados demográficos da linha de base eram comparáveis entre os grupos de vosoritida e placebo.

**Tabela 41. Características básicas dos pacientes do estudo 111-206**

Variável	Randomizado			Todos Vosoritida (n=43)
	Sentinela (n=11)	Vosoritida (n=32)	Placebo (n=32)	
Idade no Dia 1 meses, média (DP)	24.71 (20.79)	24.39 (16.83)	27.82 (19.25)	24.47 (17.66)
<b>Sexo, n(%)</b>				
Masculino	8 (72.7)	17 (53.1)	13 (40.6)	25 (58.1)

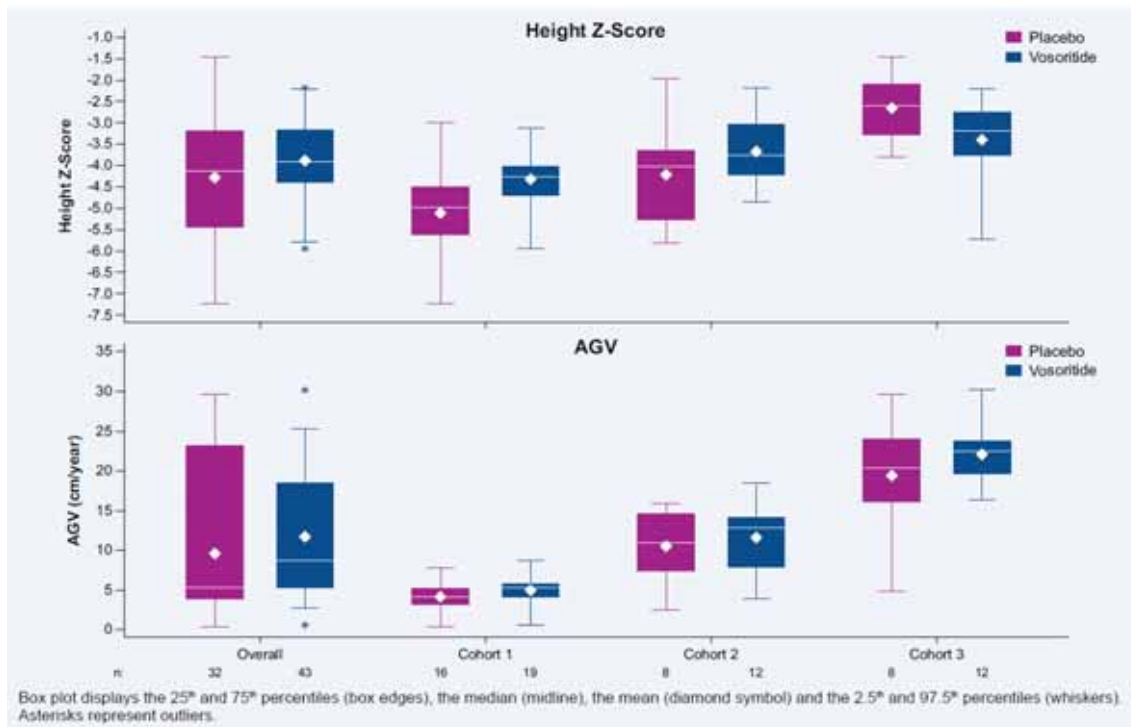


Feminino	3 (27.3)	15 (46.9)	19 (59.4)	18 (41.9)
<b>Raça, n(%)</b>				
Branco	8 (72.7)	21 (65.6)	25 (78.1)	29 (67.4)
Asiático	1 (9.1)	10 (31.3)	6 (18.8)	11 (25.6)
Outros	1 (9.1)	6 (18.8)	2 (6.3)	7 (16.3)
Japonês	0	4 (12.5)	4 (12.5)	4 (9.3)
Nativo do Havai/Ilhas do Pacífico	0	0	1 (3.1)	0
Múltiplos	2 (18.2)	1 (3.1)	0	3 (7.0)
<b>Etnia, n(%)</b>				
Não hispânico ou latino	11 (100.0)	29 (90.6)	29 (90.6)	40 (93.0)
Hispânico ou latino	0	3 (9.4)	3 (9.4)	3 (7.0)
<b>Peso, kg, média (DP)</b>	10.12 (3.70)	10.20 (3.83)	10.55 (4.31)	10.18 (3.76)
<b>Escore Z de peso, média (DP)</b>	-1.41 (0.73)	-1.49 (1.26)	-1.59 (1.44)	-1.47 (1.14)
<b>IMC, kg/m2, média (DP)</b>	20.06 (1.87)	19.48 (2.45)	20.14 (2.39)	19.63 (2.31)
<b>Escore Z do IMC, média (DP)</b>	2.79 (0.98) (n=4)	2.52 (1.15) (n=15)	2.77 (0.75) (n=16)	2.58 (1.09) (n=19)

\*As porcentagens foram calculadas usando o número total de pacientes no conjunto completo de análise (N para cada grupo de tratamento) como denominador. Abreviações; max: máximo; min: mínimo; DP: desvio padrão.

Fonte: Relatório Final de Estudo Clínico da BioMarin 111-206, 2022 [152]

**Figura 46. Características de crescimento da linha de base**



Abreviações: AGV, velocidade de crescimento anualizada.  
 Observação: O tratamento de pacientes das coortes 2 e 3 está fora da indicação atualmente licenciada e, portanto, fora do escopo desta apresentação.  
 Fonte: Pôster apresentado na Reunião Anual de 2022 da Endocrine Society, 11 a 14 de junho de 2022, Atlanta, GA, Savarirayan 2022 [132].

Como esperado, as medidas de crescimento da linha de base diferiram entre as coortes de idade e estavam alinhadas com os padrões de crescimento estabelecidos para crianças com ACH nessas faixas etárias[153]. De modo geral, o déficit médio de altura na linha de base foi maior no grupo placebo (-4,28 DP abaixo da estatura média) em comparação com o grupo totalmente com soritide (-3,88 DP abaixo da estatura média), e o VCA médio foi maior no grupo totalmente com soritide (11,66 cm/ano) em comparação com o grupo placebo (9,60 cm/ano).

### 9.2.4. Estudo 208

Os 73 participantes que concluíram o tratamento no 111-206 foram incluídos no 111-208 e receberam vosoritida.



Desses, 11 participantes tinham idade de 0 a < 6 meses (coorte 3), 22 tinham idade  $\geq 6$  a < 24 meses (coorte 2), 34 tinham idade  $\geq 24$  a < 60 meses (coorte 1) e 6 participantes tinham idade > 60 meses no início do tratamento com vosoritida (coorte 0).

Dos 73 participantes tratados, 31 haviam recebido placebo anteriormente no estudo 111-206 e 42 haviam recebido vosoritida anteriormente.

### **9.2.5. Estudo 202**

#### ***Análises***

As seguintes populações foram definidas para o período inicial de 6 meses e o período de extensão. O número de pacientes em cada população foi resumido por coorte no período inicial de 6 meses e por nível de dose no período de extensão.

População inscrita: todos os pacientes que consentiram e foram selecionados e elegíveis.

População de análise de segurança: todos os pacientes que receberam pelo menos uma dose do tratamento do estudo e foram usados para análise de segurança no período inicial de 6 meses e durante todo o período do estudo.

População de análise de segurança de extensão: todos os pacientes que receberam pelo menos uma dose do tratamento do estudo no período de extensão e foram usados para análise de segurança no período de extensão.

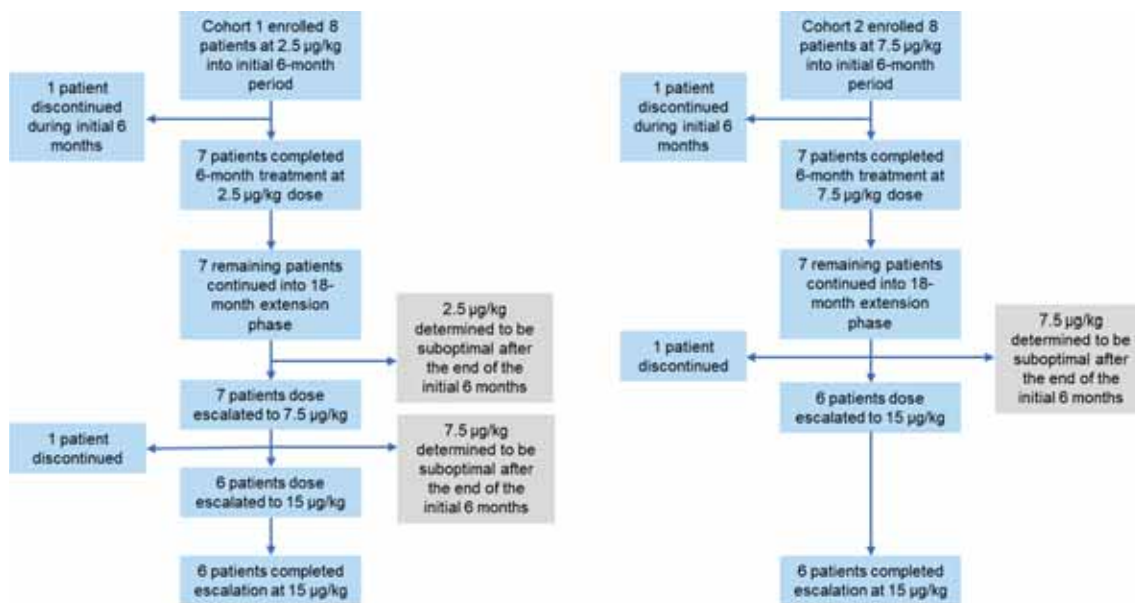
População de Análise de Eficácia: para o período inicial de 6 meses e o período de extensão, todos os pacientes que receberam pelo menos uma dose do tratamento do estudo e que tinham dados pós-tratamento para qualquer ponto final de eficácia no período correspondente foram incluídos na população de Análise de Eficácia e Análise de Eficácia de Extensão, respectivamente. População de análise farmacocinética (PK): para o período inicial de 6 meses e o período de extensão, todos os pacientes que receberam pelo menos uma dose do tratamento em estudo neste estudo e que tinham qualquer informação de PK pós-tratamento no período correspondente. Trinta e cinco pacientes com HAC participaram deste estudo; não foram realizados cálculos formais do tamanho da amostra. Os pacientes que interromperam o tratamento prematuramente após o 10º dia não foram substituídos. As datas ausentes ou parcialmente ausentes foram imputadas de forma conservadora para medicamentos concomitantes e EAs para garantir que um EA fosse considerado emergente para o tratamento e tivesse a maior



duração possível. População e disposição dos pacientes: A disposição dos pacientes em 111-202 é apresentada em

Figura 47. Um total de 35 pacientes foi inscrito; oito pacientes em cada uma das Coortes 1 e 2, dez pacientes na Coorte 3 e nove pacientes na Coorte 4. Durante o período de extensão, um paciente deixou de participar de cada uma das Coortes 1 e 2, elevando para 30 o número total de pacientes que concluíram o estudo de dois anos. Além disso, 12 pacientes das Coortes 1 e 2 foram trocados para vosoritida 15 µg/kg durante a fase de extensão do estudo .[119] As características demográficas e clínicas dos pacientes na linha de base são apresentadas na Tabela 42.

**Figura 47. Disposição do paciente para 111-202**



Fonte: Relatório de Estudo Clínico BioMarin 111-202, 2018 [119]

**Dados demográficos e características básicas dos pacientes**

Em geral, as coortes eram equilibradas em termos de dados demográficos e medidas de crescimento de linha de base (Tabela 42).

**Tabela 42. Características básicas dos pacientes no estudo 111-202**

Variável	111-202 (População de análise: segurança)				
	Coorte 1 (n=8)	Coorte 2 (n=8)	Coorte 3 (n=10)	Coorte 4 (n=9)	Todas as coortes (N=35)



<b>Idade (anos), média (DP) na triagem</b>					
<b>Idade, n (%)<sup>a</sup></b>	7.3 (1.58)	8.3 (2.19)	8.0 (1.63)	6.9 (1.17)	7.6 (1.68)
<b>≥ 5 a &lt; 8 anos</b>	6 (75.0)	3 (37.5)	4 (40.0)	5 (55.6)	18 (51.4)
<b>≥ 8 a &lt; 11 anos</b>	1 (12.5)	1 (12.5)	4 (40.0)	4 (44.4)	10 (28.6)
<b>≥ 11 a &lt; 15 anos</b>	1 (12.5)	4 (50.0)	2 (20.0)	0	7 (20.0)
<b>≥ 15 a &lt; 18 anos</b>	0	0	0	0	0
<b>Gênero, n (%)</b>					
<b>Masculino</b>	3 (37.5)	5 (62.5)	4 (40.0)	4 (44.4)	16 (45.7)
<b>Feminino</b>	5 (62.5)	3 (37.5)	6 (60.0)	5 (55.6)	19 (54.3)
<b>Branco</b>	7 (87.5)	6 (75.0)	5 (50.0)	6 (66.7)	24 (68.6)
<b>Asiático</b>	0	1 (12.5)	3 (30.0)	3 (33.3)	7 (20.0)
<b>Negro ou afro- americano</b>	1 (12.5)	0	1 (10.0)	0	2 (5.7)
<b>Outros</b>	0	1 (12.5)	1 (10.0)	0	2 (5.7)
<b>Etnia, n (%)<sup>a</sup></b>					
<b>Não hispânico ou latino</b>	8 (100.0)	8 (100.0)	9 (90.0)	7 (77.8)	32 (91.4)
<b>Hispânico ou latino</b>	0	0	1 (10.0)	1 (11.1)	2 (5.7)
<b>Não informado</b>	0	0	0	1 (11.1)	1 (2.9)
<b>Estágio de Tanner da mama (somente mulheres)</b>					



I	5 (100.0)	3 (100.0)	6 (100.0)	5 (100.0)	19 (100.0)
<b>Genitália Estágio de Tanner (somente homens)</b>					
I	2 (66.7)	5 (100.0)	4 (100.0)	4 (100.0)	15 (93.8)
<b>Não realizado</b>	1 (33.3)	0	0	0	1 (6.3)
<b>Peso (kg), n, média (DP)</b>	18.58 (2.22) (População de análise: Eficácia, n=8)	22.50 (4.10) (População de análise: Eficácia, n=8)	25.13 (5.74) (População de análise: Eficácia, n=10)	19.59 (2.86) (População de análise: Eficácia, n=8)	21.56 (4.70)
<b>IMC (kg/m<sup>2</sup>), n, média (DP)</b>	20.13 (2.09)	21.78 (2.10)	22.21 (2.69)	20.44 (1.04)	21.17 (2.18)

Fonte: Pôster ACMG 2021\_Vosoritida 60-month Update [117]

## 9.2.6. Estudo 205

### *Análises*

FAS: foi definido de acordo com o princípio de intenção de tratar e inclui todos os participantes registrados. O FAS foi usado para apresentar as características de linha de base e os dados de eficácia. Os resumos de eficácia incluem avaliações até a data de corte ou 45 dias após a interrupção do tratamento.

População de segurança: todos os pacientes na FAS que receberam pelo menos uma dose do medicamento em estudo no Estudo 111-205.

População de PK: todos os pacientes na população de segurança que têm pelo menos uma concentração de PK avaliável no Estudo 111-205.

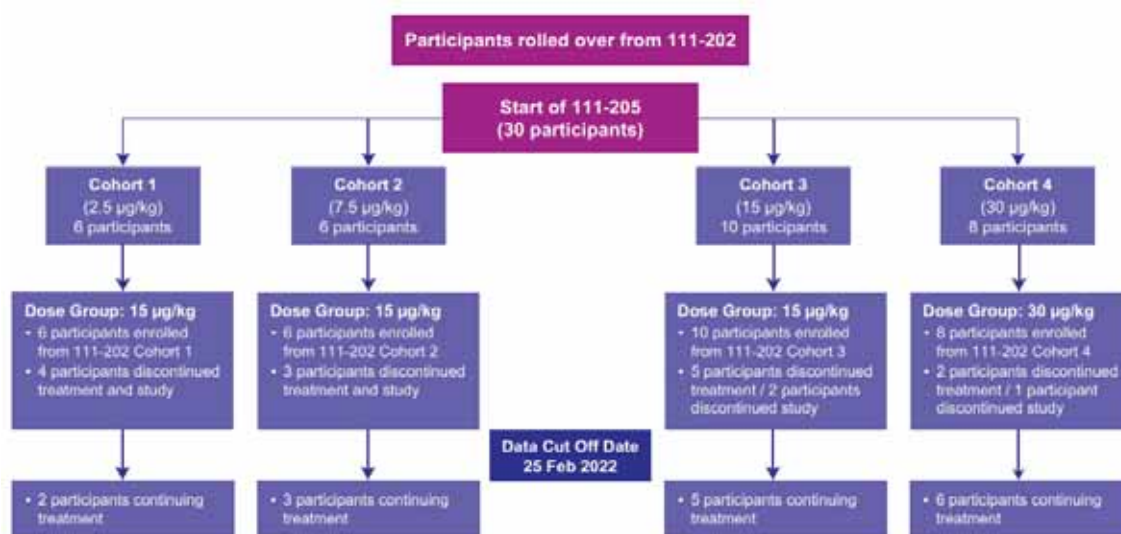
População de imunogenicidade: todos os pacientes na População de Segurança que têm pelo menos uma amostra de imunogenicidade avaliável no Estudo 111-205.

Todos os desfechos de eficácia foram avaliados na população FAS pela coorte na qual foram inscritos no Estudo 111-202 e no geral. Não foram realizados cálculos formais do tamanho da amostra. Os dados ausentes não foram imputados, exceto para datas parciais/ausentes.

### População e disposição dos pacientes

A disposição dos pacientes, por coorte, para os pacientes inscritos no estudo 111-205 é apresentada em [Figura 48](#). Trinta dos 35 pacientes do 111-202 foram incluídos no 111-205; seis pacientes em cada uma das Coortes 1 e 2, dez pacientes na Coorte 3 e oito pacientes na Coorte 4. Após 6 meses de dosagem no 111-202, os pacientes das Coortes 1 e 2 foram titulados para receber 15 µg/kg, enquanto os pacientes das Coortes 3 e 4 continuaram a receber 15 µg/kg e 30 µg/kg, respectivamente. Assim, todos os indivíduos da 111-205 receberam 15 µg/kg ou 30 µg/kg[154]

**Figura 48. Disposição do paciente para 111-202/205**



Cinco dos que descontinuaram atingiram a altura adulta final (FAH)

Fonte: Hoover-Fong et al, pôster apresentado na Reunião Anual de Genética Clínica do ACMG de [135]

### Dados demográficos

Em geral, as coortes eram equilibradas em termos demográficos e de medidas de crescimento de linha de base (os dados de linha de base do Estudo 111-205 são os mesmos do Estudo 111-202 ([Tabela 42](#)) [154]

### 9.3. ANEXO V – Descrição dos desfechos clínicos relevantes

- **Velocidade de crescimento anualizada (VCA):** demonstra quantos centímetros a criança cresceu dentro de um ano.

A VCA é um indicador-chave do crescimento esquelético por ser bem documentada na faixa etária pediátrica, altamente sensível a fatores que impactam o crescimento negativa ou positivamente e fácil e objetivamente mensurável de forma precisa e não invasiva. Em crianças de estatura média, a infância e a puberdade são períodos de rápido crescimento linear. Em bebês, a VCA média é mais alta logo após o nascimento (44 cm/ano) e então diminui até a idade de 5 anos antes de permanecer relativamente estável até a puberdade (5,5 a 7 cm/ano). Na puberdade, crianças de estatura média passam por um surto de crescimento com uma VCA de 8,3 a 9,3 cm/ano. Dados publicados mostraram que o padrão de crescimento de indivíduos com acondroplasia é semelhante ao de crianças de estatura média até a puberdade; no entanto, a magnitude do crescimento é menor em todas as faixas etárias.

- **Escore Z de altura:** o número de desvios padrão da altura real de uma criança em relação à altura mediana das crianças de sua idade, conforme determinado a partir da amostra padrão de crianças saudáveis.
  - Escore  $Z < -2$  a  $+2$ : O parâmetro (por exemplo, altura, peso ou IMC) está dentro de 2 DP da média para a população. Este é considerado o intervalo normal.
  - Escore  $Z < -2$ : O parâmetro está mais de 2 DP abaixo da média da população.
  - Escore  $Z < -3$ : O parâmetro está mais de 3 DP abaixo da média da população.

O escore Z de altura é um desfecho relevante para o paciente e melhorias neste escore demonstraram estar correlacionadas com a melhora da qualidade de vida



em indivíduos com acondroplasia. O escore Z é uma medida menos variável do que a velocidade de crescimento em crianças mais novas (<5 anos) com acondroplasia e, portanto, é mais útil para detectar diferenças na eficácia entre populações tratadas e não tratadas.

- **Proporcionalidade de segmento corporal:** demonstração do crescimento proporcional entre os segmentos superior e inferior do corpo.

Crianças de estatura média com idade <2 anos têm uma proporção do segmento superior para o inferior do corpo de ~1,4, que diminui para cerca de 1,1 entre 5-6 anos e atinge um valor final de 1 aos 10 anos. Em contraste, o crescimento desproporcional nos membros inferiores de pacientes com acondroplasia faz com que a parte superior do corpo represente uma proporção maior da altura total do que a parte inferior do corpo, o que é demonstrado por uma proporção do segmento superior para o inferior do corpo que é maior do que o valor típico de 1,4 observado em indivíduos de estatura média. A proporção do segmento superior para o inferior do corpo fornece uma avaliação se o efeito do tratamento está ocorrendo proporcionalmente na coluna e nos membros inferiores. A baixa estatura desproporcional é muito mais do que um desfecho estético, uma vez que os indivíduos têm dificuldades com o autocuidado devido ao seu alcance limitado, muitas vezes exigindo a assistência de um cuidador para a realização de atividades básicas da vida diária e de higiene pessoal [5, 29, 57, 65, 68, 71, 72, 148].

- **Qualidade de Vida (QdV / QoL):** Há uma série de instrumentos, incluindo escalas específicas da doença e medidas genéricas de qualidade de vida usadas para demonstrar o impacto em indivíduos com acondroplasia. Descritos abaixo estão os principais destes instrumentos utilizados durante o programa clínico, de forma não exaustiva.
  - **Escore QoLISSY:** medida de qualidade de vida em jovens de baixa estatura.

O questionário QoLISSY é um instrumento de avaliação de desfechos clínicos específico da doença, projetado para avaliar o impacto da baixa estatura diagnosticada na qualidade de vida relacionada à saúde (QVRS) em crianças de 4 a 18 anos com baixa estatura, com uma versão de coleta destinada a crianças e outra para pais, e perguntas em torno de sete áreas (funcionamento físico, social, emocional, capacidade de



enfrentamento, futuro, efeitos sobre os pais e esperança). A versão do relatório do paciente (idades de 8 anos ou mais) é composta por seis domínios principais, incluindo três domínios que examinam o bem-estar físico, emocional e social e três domínios adicionais (enfrentamento, crenças e tratamento). A versão dos pais (para crianças de 4 a 18 anos) é composta pelos mesmos domínios principais que a versão do relatório do paciente e inclui dois domínios adicionais somente para os pais (futuro e efeitos sobre os pais). Os itens são classificados em uma escala Likert de 5 pontos e produzem uma pontuação resumida que varia de 0 a 100, com valores mais altos indicando uma melhor qualidade de vida relacionada à saúde.

- **Pediatric Quality of Life Inventory (PedsQL 4.0):** Um questionário genérico para medir a qualidade de vida em torno de 4 áreas (funcionamento físico, emocional, social e escolar) em crianças e adolescentes, apresentando uma versão de coleta de dados destinada às crianças e outra destinada aos pais. O PedsQL é uma ferramenta que visa reconhecer os desfechos clínicos, incluindo intensidade da dor, qualidade de vida relacionada à saúde (QVRS), impacto da condição relacionada à saúde na família e satisfação dos pais com o tratamento. A pontuação varia de 0 (pior pontuação possível) a 100 (melhor pontuação possível). Os valores de referência padrão do PedsQL para qualidade de vida infantil são baseados em uma grande amostra pediátrica saudável (N = 9.566) com idade entre 2 e 18 anos para auto-relatos e relatos de pais/cuidadores.

### 9.4. ANEXO VI – Avaliação GRADE

Avaliação da certeza							Certeza
Nº dos estudos	Delimitação do estudo	Risco de viés	Inconsistência	Evidência indireta	Imprecisão	Outras considerações	
<b>Escore Z</b>							
4	ensaio clínico randomizado controlado <sup>1</sup>	não grave <sup>2</sup>	não grave	Não grave <sup>3</sup>	não grave	nenhum	⊕⊕⊕⊕ Alta qualidade
<b>Velocidade de crescimento anualizada</b>							
4	ensaio clínico não randomizado <sup>1</sup>	não grave <sup>2</sup>	não grave	Não grave <sup>3</sup>	não grave	nenhum	⊕⊕⊕⊕ Alta qualidade
<b>Relação segmento superior:segmento inferior do corpo</b>							
4	ensaio clínico não randomizado <sup>4</sup>	Grave <sup>5</sup>	não grave	Grave <sup>6</sup>	não grave	nenhum	⊕⊕○○ Baixa
<b>Qualidade de vida</b>							
4	ensaio clínico não randomizado <sup>4</sup>	Grave <sup>5</sup>	não grave	Grave <sup>6</sup>	não grave	nenhum	⊕⊕○○ Baixa
<b>Segurança e tolerabilidade</b>							
4	ensaio clínico não randomizado <sup>4</sup>	Grave <sup>5</sup>	não grave	Grave <sup>6</sup>	não grave	nenhum	⊕⊕○○ Baixa

Fonte: elaboração própria. 1. Sendo considerado apenas o estudo fase III,. 2. Estudo randomizado, cego comparado com placebo; 3. com comparação direta com cuidado padrão (placebo), 4. Foram 7 estudos incluídos, 1 randomizado fase III, 2 fase II braço único, 4 estudos de vida real. 5. Ausência de grupo de comparação, randomização, cegamento e ajustes para os fatores de confundimento; 6. sem comparação direta com cuidado padrão (placebo).



**9.5. ANEXO VII – Relatório de Progresso nº 1 do Estudo 111-606**



**Real-world effectiveness and safety of Voxzogo® in children  
with achondroplasia:  
An observational study in Brazil**

**Study 111-606**

**Progress Report Number 1**

**17 December 2024 to 19 August 2025**

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## 1. SUMMARY OF STUDY STATUS

This is the first progress report for study 111-606 ‘Real-world effectiveness and safety of Voxzogo® (vosoritide) in children with achondroplasia: An observational study in Brazil’. The report covers study progress since the study was initiated (protocol version 1.0 effective 17 December 2024) through 19 August 2025.

Voxzogo was approved by ANVISA (Agência Nacional de Vigilância Sanitária) on 29 November 2021; however, submission to CONITEC (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde) has not been performed yet.

The purpose of this study is to obtain local data to evaluate the effectiveness of Voxzogo in Brazil, a country which did not participate in clinical trials for Voxzogo. In clinical trial 111-301 the primary endpoint was annualized growth velocity (AGV), which demonstrated a statistically significant increase in AGV of 1.57cm/year among treated participants compared to placebo over 1 year (Savarirayan, 2020).

The 111-606 study has a total of six sites: two activated and recruiting, four pending ethics committee (EC) approval and/or contract agreements sign off (see [Table 1](#)). By 19 August 2025, ten participants had enrolled in the study, with the first participant joining on 8 July 2025 (see [Table 2](#)). The study is projected to complete enrolment by November 2025.

The study is progressing steadily, with ongoing efforts focused on site activation, participant enrolment, and data collection. Two interim analyses are scheduled to evaluate effectiveness using retrospective data collected from participants’ medical records. The first interim analysis will include data collected through Q3/Q4 2025. The second interim analysis will be conducted once full enrolment is achieved and will incorporate all retrospective data—covering up to six months prior to the initiation of Voxzogo treatment through to study enrolment. Final analysis is planned for Q2/Q3 2027.

## 2. INTRODUCTION

111-606 is a Phase IV, observational, multi-centre ambispective cohort study designed to evaluate the real-world effectiveness and safety of Voxzogo in children with achondroplasia (ACH) in Brazil.

Voxzogo is a commercially available treatment for patients with ACH. It is a modified recombinant human C-type natriuretic peptide, which downregulates the FGFR3 signaling cascade and counteracts the negative effects of constitutive FGFR3 gene activation on chondrocyte proliferation and differentiation. Voxzogo works by inducing the activation of the natriuretic peptide receptor type B through the action of C-type natriuretic peptide. It is given until the growth plate closes, and the patient achieves final adult height.

The primary objective of this study is to assess changes in height and growth velocity over time among children treated with commercial Voxzogo in routine clinical practice. Specifically, the study will measure outcomes such as standing height or body length, z-scores based on average stature children per Centers for Disease Control and Prevention [CDC] and for children with achondroplasia [Hoover-Fong et al, 2021], and annualized growth velocity (AGV).

Secondary objectives include evaluating changes in body mass index (BMI), weight, and body proportionality, including upper body length (e.g., sitting height) and other anthropometric measures. These outcomes will be assessed using data collected from participants' medical records and healthcare providers, following standard-of-care procedures at each institution. No protocol-mandated visits, experimental treatments, or procedures are required, and Voxzogo is not provided as part of the study—it must be prescribed and dispensed independently of study participation.

The study population includes children with a documented diagnosis of ACH confirmed by molecular testing, who have been treated with Voxzogo for at least 12 months in accordance with the approved Brazilian label. Participants will be enrolled during a 6-month period and followed prospectively for an additional 12 months, resulting in approximately 2 years of data collection per participant. The study is sponsored by BioMarin Brasil Farmacêutica Ltda and conducted under ethical and regulatory compliance, including informed consent and assent procedures.

### 3. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

A total of six study sites in Brazil were identified, approached, and agreed to participate in the study (Table 1). Three sites received Central Ethics Committee (CEC) approval, as well as Local Ethics Committee (LEC) approval where applicable.

To date, two of the six study sites have been fully activated. One site has received both CEC and LEC approval, but its clinical trial agreement (CTA) remains under review. The remaining three sites are awaiting LEC approval, with their CTAs also in review. Activation of these four sites is anticipated by September 2025 [Table 1].

Source Data Verification (SDV) visits are scheduled to occur every three months at each site to ensure consistent and accurate data entry. Additionally, monthly site contacts will be conducted between these SDV visits to maintain regular communication and oversight. Clinical Research Associates (CRAs) will be granted direct monitoring access to the patient's medical charts, with query processes in place to ensure accurate and complete data collection per the study protocol. The first SDV site monitoring visit will take place for Hospital Universitário Pedro Ernesto – UERJ.

**Table 1: Study Sites and Status to Date**

Site Name	PI	Activation Date	Ethics Committee Submission Date	Ethics Committee Approval Date	Contract Agreement status	Number of Enrolled Participants
Hospital de Clínicas de Porto Alegre	Temis Maria Felix	Active (25Jun25)	15May25	09Jun25	Fully executed (24Jun25)	3
Hospital Universitário Pedro Ernesto - UERJ	Ana Bordallo	Active (04Jul25)	28May25	23Jun25	Fully executed (23Jun25)	7
Instituto Fernandes Figueira - FIOCRUZ	Juan Llerena	Pending	20Feb25	28Apr25	In Review	0
Universidade Federal do Paraná - UFPR	Julienne Carvalho	Pending	18Jul25	Pending	In Review	0
Universidade Federal do Pará - UFPA	Lena Stilianidi Garcia	Pending	24Jul25	Pending	In Review	0
Hospital Universitário da Federal de Campina Grande	Paula Frassinetti Vasconcelos de Medeiros	Pending	04Jul25	Pending	In Review	0

#### 4. STUDY ENROLLMENT

Recruitment commenced upon activation of the first site on 08 July 2025 and is expected to continue until November 2025. As of 19 August 2025, ten participants have been enrolled. The study protocol aims to recruit a total of 50 participants. At enrollment, per the study inclusion criteria, all participants would have received Voxzogo for a minimum of 12 months following the approved (Brazilian) local label.

**Table 2: Enrollment Status**

Site	Participant	Enrollment date	Status
Hospital de Clínicas de Porto Alegre	BR-0024-001	28-Jul-25	Enrolled
	BR-0024-002	29-Jul-25	Enrolled
	BR-0024-003	18-Aug-25	Enrolled
Hospital Universitário Pedro Ernesto - UERJ	BR-0100-001	08-Jul-25	Enrolled
	BR-0100-002	11-Jul-25	Enrolled
	BR-0100-003	11-Jul-25	Enrolled
	BR-0100-004	11-Jul-25	Enrolled
	BR-0100-005	15-Jul-15	Enrolled
	BR-0100-006	18-Aug-25	Enrolled
	BR-0100-007	18-Aug-25	Enrolled

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**5. DISCUSSION**

The study is progressing steadily, with ongoing efforts focused on site activation of the remaining four sites, participant enrolment, and data collection. Two interim analyses are scheduled to evaluate effectiveness using retrospective data collected from participants' medical records. The first interim analysis will include data collected through Q3/Q4 2025. The second interim analysis will be conducted once full enrollment is achieved. This second analysis will incorporate all retrospective data—covering up to six months prior to the initiation of Voxzogo treatment through to study enrolment. Final analysis is planned for Q2/Q3 2027.

## 6. REFERENCES

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Hoover-Fong J et al. Achondroplasia Natural History Study (CLARITY): a multicenter retrospective cohort study of achondroplasia in the United States. *Genet Med*. 2021 Aug;23(8):1498-150.

Savarirayan R, Tofts L, Irving M, Wilcox W et al. Once daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomized, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet*. 2020; 396: 684-92.

Signature Page for VV-CLIN-039165 v1.0

Every: Approval Task	Viviane Wang Author Medical Scientific Director 26-Aug-2025 13:09:51 GMT+0000
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Every: Approval Task	Jeanne Pimenta Management Sr Director, Epidemiology & RWE Program 27-Aug-2025 11:28:50 GMT+0000
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# **ESTUDOS CIENTÍFICOS**



# Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial

Ravi Savarirayan, Louise Tofts, Melita Irving, William Wilcox, Carlos A Bacino, Julie Hoover-Fong, Rosendo Ullot Font, Paul Harmatz, Frank Rutsch, Michael B Bober, Lynda E Polgreen, Ignacio Ginebreda, Klaus Mohnike, Joel Charrow, Daniel Hoernschemeyer, Keiichi Ozono, Yasemin Alanay, Paul Arundel, Shoji Kagami, Natsuo Yasui, Klane K White, Howard M Saal, Antonio Leiva-Gea, Felipe Luna-González, Hiroshi Mochizuki, Donald Basel, Dania M Porco, Kala Jayaram, Elena Fishelva, Alice Huntsman-Labed, Jonathan Day

## Summary

**Background** There are no effective therapies for achondroplasia. An open-label study suggested that vosoritide administration might increase growth velocity in children with achondroplasia. This phase 3 trial was designed to further assess these preliminary findings.

**Methods** This randomised, double-blind, phase 3, placebo-controlled, multicentre trial compared once-daily subcutaneous administration of vosoritide with placebo in children with achondroplasia. The trial was done in hospitals at 24 sites in seven countries (Australia, Germany, Japan, Spain, Turkey, the USA, and the UK). Eligible patients had a clinical diagnosis of achondroplasia, were ambulatory, had participated for 6 months in a baseline growth study and were aged 5 to less than 18 years at enrolment. Randomisation was done by means of a voice or web-response system, stratified according to sex and Tanner stage. Participants, investigators, and trial sponsor were masked to group assignment. Participants received either vosoritide 15·0 µg/kg or placebo, as allocated, for the duration of the 52-week treatment period administered by daily subcutaneous injections in their homes by trained caregivers. The primary endpoint was change from baseline in mean annualised growth velocity at 52 weeks in treated patients as compared with controls. All randomly assigned patients were included in the efficacy analyses (n=121). All patients who received one dose of vosoritide or placebo (n=121) were included in the safety analyses. The trial is complete and is registered, with EudraCT, number, 2015-003836-11.

**Findings** All participants were recruited from Dec 12, 2016, to Nov 7, 2018, with 60 assigned to receive vosoritide and 61 to receive placebo. Of 124 patients screened for eligibility, 121 patients were randomly assigned, and 119 patients completed the 52-week trial. The adjusted mean difference in annualised growth velocity between patients in the vosoritide group and placebo group was 1·57 cm/year in favour of vosoritide (95% CI [1·22–1·93]; two-sided p<0·0001). A total of 119 patients had at least one adverse event; vosoritide group, 59 (98%), and placebo group, 60 (98%). None of the serious adverse events were considered to be treatment related and no deaths occurred.

**Interpretation** Vosoritide is an effective treatment to increase growth in children with achondroplasia. It is not known whether final adult height will be increased, or what the harms of long-term therapy might be.

**Funding** BioMarin Pharmaceutical.

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## Introduction

Achondroplasia is a primary skeletal dysplasia caused by heterozygous, gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene<sup>1</sup> that leads to impaired endochondral ossification. This results in various medical complications, functional limitations and psychosocial challenges.<sup>2</sup> Achondroplasia is the most common form of disproportionate short stature in humans, affecting approximately 250 000 people worldwide.<sup>3</sup> Approved therapies that specifically address the underlying pathophysiology of this condition are currently lacking.

Previous studies in mouse models that recapitulate the skeletal phenotype observed in achondroplasia

suggested that administration of vosoritide, a biological analogue of C-type natriuretic peptide, could restore and increase long-bone and craniofacial growth in these mice, through a mitogen-activated protein kinase-dependent pathway.<sup>4,5</sup> These results led to a phase 2, open-label, safety and dose finding study in 35 children aged 5 to 14 years with achondroplasia, all of whom had participated for at least 6 months in a lead-in growth study to calculate their baseline annualised growth velocity.<sup>6</sup> This trial had an open-label, sequential cohort design to evaluate the safety and tolerability of vosoritide administered by daily subcutaneous injection at escalating doses of 2·5, 7·5, 15·0, and 30·0 µg/kg of bodyweight. Administration of vosoritide at the doses

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This online publication has been corrected. The corrected version first appeared at thelancet.com on October 8, 2020

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## Research in context

### Evidence before this study

We searched PubMed on April 6, 2020, for original research and review articles published in English since January, 2000, with the following search terms: “achondroplasia”, “C-natriuretic peptide”, “growth hormone”, “FGFR3”, “management”, AND “treatment”. The literature indicates that treatment of achondroplasia, to date, has been solely focused on management of symptoms. Research is focusing on the therapeutic manipulation of fibroblast growth factor receptor 3 (FGFR3) activity with C-type natriuretic peptide, as this might be associated with increased skeletal growth. Human growth hormone has been administered to children with achondroplasia but does not have a significant or durable effect on growth or on final height and has unknown effects on body proportionality. A precision therapy to address the pathogenesis of this condition has been lacking. C-type natriuretic peptide is a potent stimulator of endochondral ossification through downregulation of the intracellular signalling pathway of the FGFR3 receptor. Achondroplasia is caused by a gain-of-function mutation in the *FGFR3* gene, which results in constitutive overactivity of the receptor and impaired endochondral ossification. The first clinical trial to assess the safety of administration of the C-type natriuretic peptide analogue, vosoritide, was done in 35 children with achondroplasia, and reported in 2019. This phase 2, dose-finding study showed a generally mild side-effect profile and dose-related increases in annualised growth velocity. Limitations of this study were that participants acted as their own controls with regard to growth velocity comparisons, and that the design was open-label, with no placebo group enrolled.

### Added value of this study

To our knowledge, this study is the first phase 3, randomised, double blind, placebo-controlled study done to assess the effect of vosoritide on growth in children with achondroplasia.

Children administered vosoritide had a highly significant and potentially clinically important increase in annualised growth velocity over baseline after 1 year of treatment as compared with those who received placebo with similar adverse effect profiles. We believe that this study provides the first (level 1) randomised controlled trial evidence that vosoritide effectively enhances growth of children aged from 5 to less than 18 years with achondroplasia.

### Implications of all the available evidence

This randomised controlled study provides strong evidence that daily subcutaneous administration of vosoritide (at a dose of 15.0 µg/kg of bodyweight) has a significant effect on growth velocity in children with achondroplasia aged 5 to less than 18 years. The balance of benefits and harms reported here are consistent with the previously published phase 2, open-label dose-finding studies. The children enrolled in these studies will be followed until they achieve final adult height to assess durability of response and whether a pubertal growth velocity increase is restored (as it is normally absent in children with achondroplasia). Studies are also under way to assess the use of vosoritide in children aged 0 to <5 years to evaluate whether earlier treatment will lead to better outcomes in terms of final height, body segment proportionality, and other comorbidities observed such as symptomatic foramen magnum stenosis, sleep disordered breathing, and spinal canal stenosis. We believe that this study provides the first, robust evidence for an effective, precision therapy for achondroplasia, underpinning a fundamental change in the clinical management policies, natural growth history, and treatment recommendations for children affected by this condition. It will serve as a benchmark against which other, emerging precision therapies for achondroplasia (including tyrosine kinase inhibitors, long acting forms of C-type natriuretic peptide, and fibroblast growth factor receptor ligand traps) can be measured.

tested in these children was associated with a side-effect profile that was generally mild, and it resulted in sustained dose-related increases in annualised growth velocity for up to 42 months in patients compared with their baselines. The annualised growth velocity observed in patients who received doses of 15.0 µg/kg per day and 30.0 µg/kg per day were similar, and approximated those of age-matched, average-statured children.

The balance of benefits and harms from this study supported selection of the 15.0 µg/kg-per-day dose for further investigation of vosoritide in children with achondroplasia in larger, randomised controlled studies.

This study aimed to assess the change from baseline in mean annualised growth velocity (at 52 weeks) in patients administered vosoritide as compared with controls who received placebo injections.

## Methods

### Study design

This phase 3, randomised, double-blind, placebo-controlled, multicentre trial (study 111-301) compared once-daily subcutaneous administration of vosoritide, at a dose of 15.0 µg/kg of bodyweight, with placebo in children with achondroplasia. The trial was done in hospitals at 24 study sites in seven countries (Australia, Germany, Japan, Spain, Turkey, the USA, and the UK). The studies were done in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by the relevant ethics boards at each site.

### Participants

Eligible children were aged 5 to less than 18 years, had completed at least 6 months of a lead-in, observational growth study (study 111-901; ClinicalTrials.gov number,

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NCT01603095), and were ambulatory. The clinical diagnosis of achondroplasia was confirmed by genetic testing in all patients. Patients with radiographic evidence of closed growth plates, planned bone surgery, severe untreated sleep apnoea, and other medical conditions or treatments known to affect growth were excluded. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate, before enrolment. The protocol is included in the appendix.

See Online for appendix

### Randomisation and masking

In this double-blind trial, patients were randomly assigned 1:1 to receive either vosoritide or matched, identical placebo. Randomisation was done with the use of an interactive, automated voice-response or web-response system run by ALMAC with stratification according to sex and Tanner stage (either Tanner stage 1, or Tanner stage more advanced than stage 1). No more than 20% of the total number of enrolled patients were prespecified to be more advanced than Tanner stage 1. SAS version 9.3 was used to create the randomisation list with block size 4 applied within each strata. A separate randomisation was done for the seven Japanese participants to assure that the Japanese participants were balanced across treatment arms. Participants, investigators, caregivers administering injections, and assessors analysing outcome data were all masked to group assignment. The randomisation list was received by the BioMarin Biometrics group after the final database lock.

### Procedures

Patients received either vosoritide 15·0 µg/kg or placebo, as allocated, for the duration of the 52-week treatment period administered by daily subcutaneous injections in their homes by trained caregivers. The dosing schedule was a single, daily subcutaneous injection given 7 days a week, with site rotation. Vosoritide or placebo were initially administered by site staff in the clinic. After patients were seen to be tolerating vosoritide or placebo and specified criteria had been met, trained caregivers were authorised to administer vosoritide or placebo at home. Participants were required to attend the study site for scheduled visits at screening, days 1, 2, 3, and 10, week 6, and months 3, 6, 9, and 12. Full medical clinical assessments were done at each visit in addition to vital sign assessment and anthropometric measurements. For full study assessments, see protocol in the appendix (p 34). The funder or its designee provided the study sites with a supply of investigational product sufficient for the completion of the study.

An electronic data capture system, Medidata Rave, was used to collect study data at each site. Data was entered into the electronic data capture system by site staff, source data was verified by the site responsible clinical research associate and all data was reviewed and cleaned by means

of a combination of electronic edit checks, manual checks, and data listing review. Serious adverse events were all reconciled against the content of the Argus safety database and all medical conditions and medications were coded with Medidata Coder by means of MedDRA v22.0 and WHO Drug B3 Global, March 2019 dictionaries. External vendor data underwent formal reconciliation procedures on receipt and all data stored within the electronic data capture system was approved via eSignature by each site's principal investigator. The study database was locked on Dec 5, 2019.

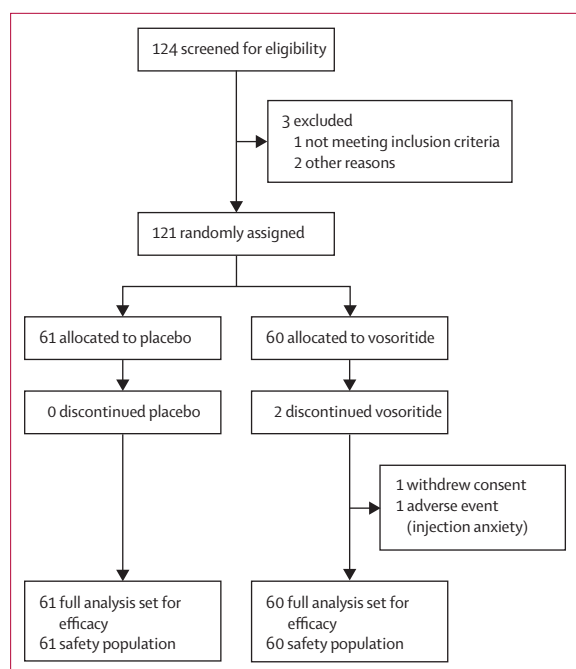
### Outcomes

The primary efficacy outcome was change from baseline in annualised growth velocity at 52 weeks in patients administered daily subcutaneous injections of vosoritide compared with controls who received placebo injections. Key secondary outcomes comprised: change from baseline in height Z score and change from baseline in upper to lower segment body ratio. Other secondary outcomes comprised evaluation of the safety and tolerability of vosoritide; evaluation of the pharmacokinetics and immunogenicity of vosoritide; and evaluation of change from baseline in bone metabolism markers including serum collagen type X marker, a biomarker of endochondral ossification.<sup>7</sup> Initial exploratory endpoints comprising, change from baseline in extremity body proportion ratios, evaluation of effect of vosoritide on bone quality, evaluation of potential changes in health-related quality of life, and evaluation of potential changes in functional independence, were changed to secondary endpoints during the trial by protocol amendment (on Feb 1, 2019), owing to their potential clinical importance and health authority feedback.

Harms were evaluated by the incidence of adverse events, serious adverse events, laboratory test results, vital signs, physical examination, electrocardiogram and echocardiogram results, clinical hip assessment, and antivosoritide immunogenicity responses. Imaging assessments provided measurements of the spine and long bones of the arms and legs, along with data regarding growth plate, bone mineral density and bone age (see appendix p 6).

### Statistical analysis

With 55 patients planned in each of the two randomised groups, the power to detect a difference of 1·75 cm/year between the vosoritide group and the placebo group in change from baseline in annualised growth velocity at 12 months was approximately 90%. This assumed the pooled SD of the change from baseline in annualised growth velocity was 2·80 cm/year, using a two-sided, two-sample *t* test at the 0·05 significance level. The power calculation was based on data from the phase 2, open-label, study of vosoritide in children with achondroplasia.<sup>6</sup> All analyses were done with SAS version 9.4, using the Proc MIXED procedure.



**Figure 1: Trial profile**

Once the 52-week placebo-controlled study was completed, 119 patients had enrolled in the ongoing extension study, in which all participants are receiving vosoritide (study 111-302; ClinicalTrials.gov number, NCT03424018).

All randomised and consented patients, constituting the full analysis set, were included according to intention-to-treat principles for the efficacy analyses ( $n=121$ ). All patients who received at least one dose of vosoritide or placebo ( $n=121$ ) were included in the safety analyses. Baseline annualised growth velocity was calculated from standing height measured over the last 6 months of the run-in study. Post-baseline annualised growth velocity was calculated from standing height at 52 weeks, and then summarised by treatment group. Change from baseline in annualised growth velocity was derived for each patient as the difference between the post-baseline and baseline annualised growth velocity. This individual patient data for the 121 randomised patients was then assessed in the ANCOVA model. Standing height was converted to an age-appropriate and sex-appropriate Z score by comparison with Centers for Disease Control and Prevention reference standards.<sup>8</sup> The upper to lower body segment ratio was calculated as the ratio between sitting height and standing height minus sitting height. The overall type I family-wise error rate for testing the primary and key secondary efficacy endpoints using an ANCOVA model was controlled at the two-sided 0.05 significance level using a three-step serial gatekeeping multiple comparisons procedure. Following this multiple comparisons procedure, advancement to the next step only occurred if the null hypotheses within a step and the previous step(s) were all rejected at the significance level of 0.05

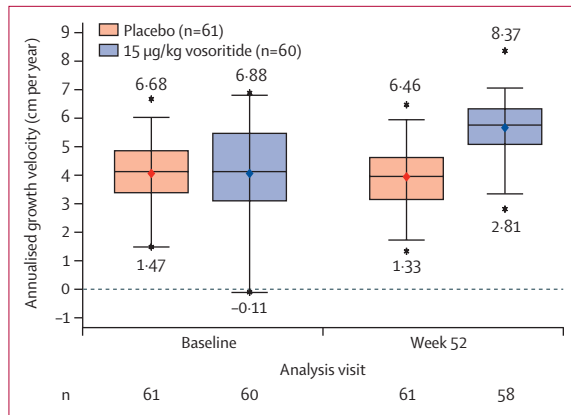
	Placebo (n=61)	15 µg/kg vosoritide (n=60)
Age at day 1 (years)	9.06 (2.47)	8.35 (2.43)
Sex*		
Female	28 (46%)	29 (48%)
Male	33 (54%)	31 (52%)
Race*		
White	41 (67%)	45 (75%)
Ethnicity*		
Not Hispanic or Latino	55 (90%)	59 (98%)
Annualised growth velocity, cm/year		
Mean	4.06 (1.20)	4.26 (1.53)
Median	4.13	4.14
25th, 75th percentile	3.40, 4.86	3.10, 5.47
Minimum, maximum	1.5, 6.7	-0.1, 6.9
Height Z score		
Mean	-5.14 (1.07)	-5.13 (1.11)
Median	-5.15	-5.27
25th, 75th percentile	-5.78, -4.44	-5.93, -4.39
Minimum, maximum	-7.9, -2.7	-7.7, -1.1
Upper to lower body segment ratio		
Mean	2.01 (0.21)	1.98 (0.20)
Median	1.99	2.01
25th, 75th percentile	1.90, 2.12	1.89, 2.13
Minimum, maximum	1.5, 2.6	1.3, 2.3
Standing height		
Mean	102.94 (10.98)	100.20 (11.90)
Median	104.63	98.58
25th, 75th percentile	94.10, 111.47	90.82, 105.68
Minimum, maximum	79.9, 129.3	80.1, 136.8

Data are n (%) or mean (SD). \*Percentages were calculated using the total number of patients in the full analysis set (n for each treatment group) as the denominator. No missing data for any of the variables.

**Table 1: Baseline characteristics (full analysis set)**

in favour of vosoritide. If any null hypothesis within a step was not rejected or was rejected but not in favour of vosoritide, the hypothesis tests corresponding to all subsequent steps would not be considered confirmatory. All hypothesis tests were two-sided. The models which tested the treatment difference always included the following baseline covariates: strata (male Tanner stage I, female Tanner stage I, male Tanner Stage >I, female Tanner Stage >I); age, annualised growth velocity and height Z score.

As specified in the statistical analysis plan, a multiple imputation procedure, namely, PROC MI would be used for the primary endpoint analysis to account for missing data. However, in the event that there was insufficient data to apply this procedure, then a pre-specified alternative approach would be used by applying the baseline annualised growth velocity to the last available height assessment. As there were only two patients with missing data, this imputation approach was therefore used for the primary endpoint analysis.



**Figure 2: Box and whisker plot of annualised growth velocity at baseline and 52 weeks by treatment arm**

Red boxes represent annualised growth velocity for patients in the placebo study treatment arm and blue boxes represent annualised growth velocity for patients in the vosoritide study treatment group. Baseline annualised growth velocity was established using data from the last 6 months of the observational run-in study before the screening visit. Annualised growth velocity at the week 52 visit was based on standing height calculated as [(height at week 52 visit – height at baseline visit) / (date at week 52 visit – baseline visit date)] × 365.25. Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers). \*Outliers.

	Placebo (n=61)	Vosoritide (n=60)	Difference in least-squares means*	Two-sided p value
<b>Primary endpoint change from baseline in annualised growth velocity</b>				
Least-squares mean change from baseline	0.13 (-0.18 to 0.45)	1.71 (1.40 to 2.01)	1.57 (1.22 to 1.93)	p<0.0001
<b>Key secondary endpoint change from baseline in height Z score</b>				
Least-squares mean change from baseline	-0.01 (-0.10 to 0.09)	0.27 (0.18 to 0.36)	0.28 (0.17 to 0.39)	p<0.0001
<b>Key secondary change from baseline in upper to lower body segment ratio</b>				
Least-squares mean change from baseline	-0.02 (-0.05 to 0.01)	-0.03 (-0.06 to 0.00)	-0.01 (-0.05 to 0.02)	p=0.51
Data are least-squares means (95% CI). *Difference is 15 µg/kg vosoritide minus placebo. Missing standing height at week 52 (ie, day 365) will be imputed by applying the baseline annualised growth velocity (cm/year) to the last available height. Least-squares means and difference in least-squares means were obtained from an ANCOVA model. Model terms included stratum defined by sex and Tanner stage, treatment, baseline age, baseline annualised growth velocity, baseline height Z score (and in the case of upper to lower body segment ratio, baseline body ratio was also included). Annualised growth velocity at a post-baseline visit is defined as [(height at post-baseline visit – height at baseline) / (date of post-baseline visit – date of baseline assessment)] × 365.25.				
<b>Table 2: Analysis of covariance of primary and key secondary endpoints (full analysis set)</b>				

The two patients in the vosoritide treatment arm, without a standing height assessment at week 52, had their missing standing height at week 52 imputed by applying baseline annualised growth velocity to the last available height assessment. Subsequently, these imputed standing height values were used to calculate their annualised growth velocity and height Z score at week 52.

Sensitivity analyses, where an alternative multiple imputation procedure (a washout model) was used to account for the missing assessment data of those patients (n=2) who discontinued the trial before 52 weeks of participation, are described in the Appendix (p 9).

Six prespecified subgroup analyses were also done on each of the primary, and two key secondary efficacy endpoints. Forest plots provide an overall summary for the primary and key secondary endpoints, and of each subgroup, showing the difference between the treatment group least-squares mean change from baseline and the 95% CI for the difference, at week 52 (see appendix pp 224–303).

The safety population was defined as all patients in the full analysis set who received at least one dose of vosoritide or placebo. Safety was assessed by examining the incidence, severity (determined using the Common Terminology Criteria for Adverse Events, version 4), and relationship to study drug of all treatment-emergent adverse events was reported during the study period. In addition, changes from baseline in clinical laboratory results and vital signs were assessed. Summary tables by treatment group included all safety events up to 30 days following treatment discontinuation (see appendix pp 27–32).

An independent Data Monitoring Committee overiewed the study, and reviewed all safety data every 6 months. The trial was first registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT number, 2015-003836-11) on Oct 20, 2016, and the first patient was enrolled into the trial on Dec 12, 2016.

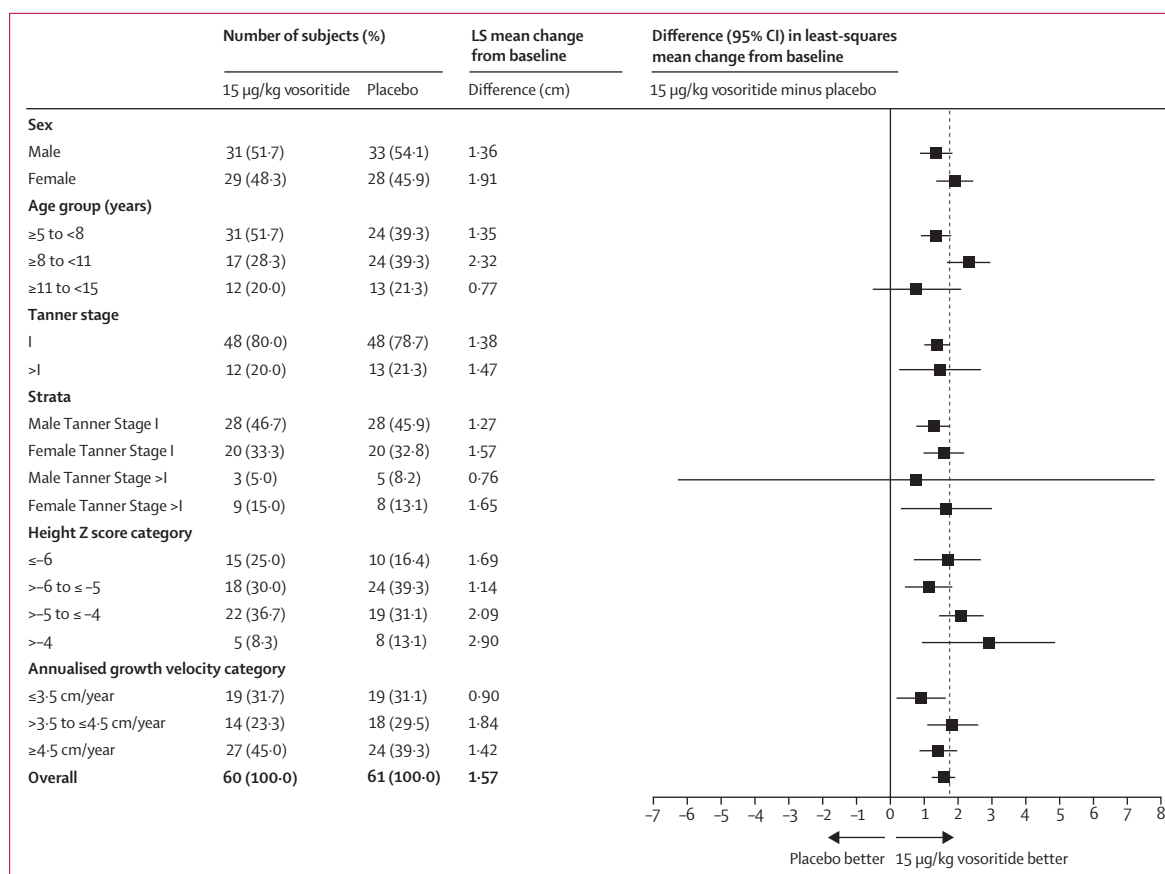
**Role of the funding source**

The funder designed the studies with input from the investigators, provided the study medication and matching placebo, and analysed the data collected from the trial sites. Confidentiality agreements were in place between the funder and the investigators. The corresponding author had full access to the data in the study and made the decisions concerning the content of the submitted manuscript. All authors reviewed the manuscript before submission for publication and approved its submission.

**Results**

Participants were recruited to this trial between Dec 12, 2016, and Nov 7, 2018. 124 patients were screened for eligibility (figure 1) with 121 assessed as eligible (57 female patients, 64 male patients). These patients were enrolled and randomly assigned, with 60 assigned to receive vosoritide and 61 to receive placebo. The baseline characteristics were similar between the two treatment groups (table 1). As of Oct 31, 2019, the 52-week placebo-controlled study was completed, and 119 patients had enrolled in the extension study, in which all participants are receiving vosoritide (study 111-302; ClinicalTrials.gov number, NCT03424018). During the 52-week study, two patients in the vosoritide group discontinued, one after 2 days owing to pain from injections and one after 6 days owing to fear of needles (figure 1).

All randomised patients were included in the efficacy analyses, using an ANCOVA model including four covariates that adjusted for baseline differences between



**Figure 3:** Forest plot of least-squares mean difference in mean change from baseline in annualised growth velocity at week 52 by subgroup. ANCOVA models were applied to determine the least squares mean change from baseline treatment difference at 52 weeks and 95% CIs. All models provide the treatment difference adjusted for the following baseline covariates: strata: (male Tanner stage I, female Tanner stage I, male Tanner stage >I, female Tanner stage >I); age; annualised growth velocity; and height Z score. Subgroup analyses were done by applying the ANCOVA model used for the primary analysis to each subgroup category. The vertical dashed line represents the change from baseline difference of 1.75 cm/year for which the study was powered.

treatment groups. After 52 weeks of treatment, there was an increase in annualised growth velocity in patients treated with vosoritide versus placebo of 1.57 cm/year, (95% CI 1.22–1.93, with a two-sided p-value of <0.0001) (see figure 2, table 2, and appendix p 17). At the 15.0 µg/kg dose, the least-squares mean change from baseline that adjusted for baseline differences between the treated and placebo groups represented a 1.71 cm/year (95% CI 1.40 to 2.01) change from baseline annualised growth velocity versus 0.13 cm/year (95% CI –0.18 to 0.45) for placebo. Serum collagen type X marker concentrations, a real-time marker of endochondral ossification, were elevated through 52 weeks in vosoritide treated patients versus placebo (appendix p 10). Bone age progressed normally in both study arms (appendix pp 11, 12), and dual energy x-ray absorptiometry showed no significant changes in bone mineral content or bone mineral density over the 52-week trial period in either the treatment or the placebo group (data not shown).

The results of the subgroup analyses for change from baseline in annualised growth velocity are summarised in figure 3. All estimates of the mean difference between

treatment groups are in the favour of vosoritide and all 95% CIs are overlapping.

Height Z score was analysed using the same methods as the primary analysis. The least-squares mean difference between vosoritide and placebo at week 52 was +0.28 in favour of vosoritide (95% CI 0.17–0.39, two-sided p value <0.0001; see table 2, appendix p 13). Prespecified, three-step serial gatekeeping was applied and since the primary endpoint test was positive, the type I error rate was controlled for testing on this key secondary endpoint. The results of the subgroup analyses show that all estimates of the mean difference between treatment groups are greater than or equal to zero and the 95% CIs are overlapping (see appendix p 14).

The change from baseline in upper to lower body segment ratio was also analysed using the same methods as the primary analysis. The least squares mean difference in change from baseline between vosoritide and placebo at week 52 was –0.01 (95% CI –0.05–0.02; two-sided p=0.51; see table 2, appendix pp 15, 16). Change from baseline in extremity body proportion ratios, including lower limb, upper limb, and arm span, also showed no

	Placebo (n=61)		15 µg/kg vosoritide (n=60)	
	Incidence*	Event rate†	Incidence*	Event rate†
Total treatment exposure, person-years	..	60.93	..	57.99
Patients with event of special interest				
Fractures	0	0	1 (2%)	1 (0.02)
Slipped capital femoral epiphysis	0	0	0	0
Avascular necrosis or osteonecrosis	0	0	0	0
Patients with any serious adverse event				
Influenza	0	0	1 (2%)	1 (0.02)
Appendicitis	1 (2%)	1 (0.02)	0	0
Radius fracture	0	0	1 (2%)	1 (0.02)
Adenoidal hypertrophy	1 (2%)	1 (0.02)	1 (2%)	1 (0.02)
Sleep apnoea syndrome	0	0	1 (2%)	1 (0.02)
Dyspnoea	1 (2%)	1 (0.02)	0	0
Intracranial pressure increased	1 (2%)	1 (0.02)	0	0
Spinal cord compression	1 (2%)	1 (0.02)	0	0
Patients with any adverse event				
Injection site reaction	60 (98%)	2121 (34.8)	59 (98%)	7345 (126.7)
Injection site erythema	29 (48%)	229 (3.8)	44 (73%)	2280 (39.3)
Injection site swelling	40 (66%)	1215 (19.9)	41 (68%)	3987 (68.7)
Nasopharyngitis	6 (10%)	53 (0.9)	23 (38%)	322 (5.6)
Vomiting	18 (30%)	29 (0.5)	16 (27%)	26 (0.4)
Headache	12 (20%)	16 (0.3)	16 (27%)	25 (0.4)
Pyrexia	16 (26%)	30 (0.5)	14 (23%)	23 (0.4)
Arthralgia	13 (21%)	22 (0.4)	10 (17%)	11 (0.2)
Injection site urticaria	4 (7%)	7 (0.1)	9 (15%)	11 (0.2)
Upper respiratory tract infection	2 (3%)	5 (0.1)	8 (13%)	71 (1.2)
Blood pressure decreased	10 (16%)	12 (0.2)	8 (13%)	8 (0.1)
Cough	3 (5%)	3 (0.05)	7 (12%)	10 (0.2)
Diarrhoea	8 (13%)	10 (0.2)	7 (12%)	8 (0.1)
Ear infection	2 (3%)	2 (0.03)	6 (10%)	8 (0.1)
Ear pain	6 (10%)	6 (0.1)	6 (10%)	8 (0.1)
Influenza	3 (5%)	3 (0.05)	6 (10%)	11 (0.2)
Oropharyngeal pain	3 (5%)	3 (0.05)	6 (10%)	8 (0.1)
Otitis media	4 (7%)	4 (0.1)	6 (10%)	13 (0.2)
	6 (10%)	9 (0.1)	6 (10%)	7 (0.1)

Data are n (%) or m (rate). Adverse events with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation were included. Adverse events were coded using Medical Dictionary for Regulatory Activities version 22.0. \*Percentages were calculated using the total number of patients in the safety population (n for each treatment group) as the denominator. Patients with more than one adverse event of the same preferred term were counted only once for that preferred term. †Exposure-adjusted event rates were calculated by dividing the total number of events (m) by the total treatment exposure in each treatment group. Multiple occurrences of an adverse event with the same preferred term for a patient were counted for each occurrence for that preferred term.

**Table 3: Incidence and exposure-adjusted event rates for common (≥10%) treatment-emergent adverse events in the vosoritide treatment group, all serious adverse events, and events of special interest (full safety population)**

difference (data not shown). For the secondary endpoint of standing height see the appendix (p 20).

No clinically meaningful differences were observed in change from baseline between the placebo and vosoritide groups in health-related quality of life, assessed by the Pediatric Quality of Life Inventory (PedsQL), and the Quality of Life of Short Statured Youth (QoLISSY) tools,

or functional independence, as assessed by the Functional Independence Measure for children (WeeFIM), after completion of the 52-week study period (see appendix pp 6, 21–25).

Sensitivity analyses using a multiple imputation washout model to impute missing assessments for two patients who discontinued treatment before 52 weeks were consistent with the main results (see appendix p 26). SAS procedure Proc MI with the missing-not-at-random option was used for the washout model, which only used placebo data to impute the missing week 52 assessment.

Common treatment-emergent adverse events are shown in table 3 and all adverse events are shown in the appendix (pp 28–32). Most adverse events were mild with no new safety findings. Injection site reactions were most commonly reported and were all non-serious and transient. Additionally, there were no grade 3 or higher hypersensitivity reactions, or anaphylaxis reported. Blood pressure and pulse rate were monitored frequently during the initial study visits, for 2 h post-dose during the first 3 days of treatment, and for 1 h on subsequent visits. No clinically significant cardiovascular changes were observed and post-dose decreases in systolic blood pressure <70 mm Hg (plus two times age) were reported in 14 (23%) of 60 patients on vosoritide treatment and 15 (25%) of 61 on placebo, whereas post-dose decreases in diastolic blood pressure less than 40 mm Hg were reported in 10 (17%) of 60 patients receiving vosoritide and six (10%) of 61 receiving placebo (appendix p 27).<sup>9</sup> All changes in blood pressure were asymptomatic, except for one patient treated with vosoritide, who had a single symptomatic hypotensive event associated with sitting up suddenly before a blood draw (associated with a post-dose systolic blood pressure decrease of <20 mm Hg, and a diastolic decrease of <10 mm Hg), which was transient and resolved without medical intervention.

A total of nine serious adverse events were reported in seven patients, which included four patients on placebo with grade 3 appendicitis, grade 3 adenoidal hypertrophy, grade 2 dyspnoea, grade 3 intracranial pressure increased, and grade 3 spinal cord compression, and three patients on vosoritide with grade 3 influenza, grade 3 radial fracture, grade 2 adenoidal hypertrophy and grade 3 sleep apnoea syndrome. None of the serious adverse events were considered by the investigator to be related to study drug and no deaths occurred. There were no adverse events related to disproportionate skeletal growth.

Serum immunogenicity samples for assessment were collected predose at baseline and every 12 weeks through to the end of the study. Serum total antidrug antibody titres were detected in 42% of patients (25 out of 60) at one or more assessment visits. Serum total antidrug antibody titres were positive either at a single visit (n=8) or two or more visits (n=17) during the study. No neutralising antibodies were detected in any patients. There was no association between the presence of total antidrug antibodies and change in annualised growth

velocity or frequency or severity of hypersensitivity or injection site reactions.

## Discussion

In this phase 3 trial, vosoritide, administered to children with achondroplasia at a dose of 15.0 µg/kg per day resulted in a highly significant increase in annualised growth velocity and height Z scores after 52 weeks of treatment as compared with placebo. There were no adverse effects on, or significant improvements in upper to lower body segment proportionality in children receiving vosoritide during this 52 week study. This suggests that either a longer treatment period or earlier treatment initiation might be required to detect these changes. These data are consistent with those observed in the phase 2 trials of vosoritide,<sup>6</sup> and provide further clinical evidence that vosoritide represents the first therapy to address the underlying molecular pathology in individuals with achondroplasia. The absence of any observed adverse effects on bone maturation or upper to lower body segment proportionality strengthens the prediction that longer periods of treatment might result in durable and proportionate effects on skeletal growth, leading to increased final adult height. Human growth hormone, which is approved for use in achondroplasia in Japan, has failed to show durable or significant effects on growth and final adult height,<sup>10</sup> and does not address the underlying pathogenesis.

This study is limited in that direct evaluation of the effect of vosoritide treatment on final adult height and how this relates to functionality, quality of life, and activities of daily living in people with achondroplasia cannot be evaluated at this time. In addition, whether treatment with vosoritide will ameliorate the medical complications associated with achondroplasia and decrease the need for surgical interventions is unknown.

Concerns around these limitations are shared by some in the short-statured community, and their support groups, who consider that a treatment that only increases height in achondroplasia is not a priority, and that the short-term and long-term health of individuals must also be enhanced. These perspectives are balanced by the views of some participants in this trial and their families, who agree that while better health is an important outcome, increased height in itself will facilitate better access to the environment, less discrimination, and higher self-esteem.

To address these limitations, concerns, and unanswered questions, an ongoing, open-label, phase 3, extension study (ClinicalTrials.gov number, NCT03424018) will continue to evaluate the balance of benefits and harms of vosoritide until the patients reported in this study reach final adult height. This study will collect data regarding vosoritide therapy on wider health measures including quality of life, activities of daily living, and frequency and type of medical and surgical interventions compared with registry data of untreated children with achondroplasia. This long-term study will also provide data on whether

treatment of children with achondroplasia with vosoritide will result in a pubertal growth spurt, which appears to be absent in this condition<sup>11</sup> and provide the opportunity to detect any harms associated with long-term therapy.

In addition, a phase 2, randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov number, NCT03583697) of vosoritide in infants and younger children (aged 3 months to <60 months) with achondroplasia has been designed to provide further insights into the long-term treatment effects on body proportionality and growth, as well as how earlier treatment might affect the most substantial medical complications (eg, foramen magnum stenosis with brainstem compression).

No new harms associated with vosoritide treatment were identified in this trial. There was no difference in the incidence of side-effects between the treated and control groups, no drug-related serious adverse events, and the safety profile of vosoritide remained generally mild (table 3). Given the concern regarding the vascular side-effects of vosoritide, based on the structural similarity of C-type natriuretic peptide with atrial natriuretic peptide, pulse rate and blood pressure were monitored frequently in this trial (see appendix p 75). Vosoritide administration was associated with mild, transient, and clinically inconsequential blood pressure changes, that were self-limiting. These results are consistent with those observed in the phase 2 studies of vosoritide and strengthen its vascular safety profile.

It is noteworthy that another C-type natriuretic product (TransCon CNP), with a longer half-life than vosoritide, and engineered to be administered as a weekly subcutaneous injection, is undergoing clinical development for the treatment of children with achondroplasia.<sup>12</sup> Other therapies that address the underlying pathogenesis of achondroplasia, including a soluble FGFR3 molecule used as a ligand trap<sup>13</sup> (recifercept), and a selective oral tyrosine kinase/FGFR3 inhibitor<sup>14</sup> (infigratinib), have shown efficacy in mouse models of achondroplasia and are now in early clinical development. It will be of interest to compare the safety and efficacy profiles of these potential therapeutic options with vosoritide as they progress through clinical trials, and whether any of their actions might be synergistic for possible future combination therapy.

In summary, daily subcutaneous administration of vosoritide to children with achondroplasia resulted in significantly increased growth velocity and height Z scores. There were no adverse effects on upper to lower body segment proportionality or bone maturation, and vosoritide was otherwise generally well tolerated. The vascular effects were mild, generally clinically inconsequential, and self-limiting.

To our knowledge, this study provides the first, robust evidence for an effective, precision therapy for achondroplasia that could fundamentally change the clinical management policies, growth trajectory, and treatment recommendations for children affected by this condition. It is envisaged that the results reported in this study

establish vosoritide as the first, precision treatment option in the care of children with achondroplasia.

#### Contributors

RS wrote the first draft of the manuscript, assisted by JD. JD, DMP, KJ, and EF wrote the first draft of the protocol and amendments with input from RS, MI, and JH-F. AH-L did the statistical analysis. RS, LT, MI, WW, CAB, JH-F, RUF, PH, FR, MBB, LEP, IG, KM, JC, DH, KO, YA, PA, SK, NY, KKW, HMS, AL-G, FL-G, HM, and DB recruited and enrolled patients to the trial, and managed them during the trial period according to the protocol. RS and JD vouch for the data as reported, adherence of the trial to the protocol, and complete reporting of all adverse events.

#### Declaration of interests

All authors were investigators in this clinical trial with the exception of DMP, KJ, EF, AH-L, and JD, who are employees of the funder (BioMarin). RUF, IG, KO, YA, DH, SK, NY, HMS, AL-G, FL-G, and HM declare no conflicts of interest. RS, LT, FR, and KM have received consulting fees and grants from BioMarin. MI and WW have received consulting fees from BioMarin. JC and DB have received grants from BioMarin. LEP and PA have received honoraria from BioMarin. CAB and PH have received consulting fees, honoraria and grants from BioMarin. JH-F has received consulting fees from BioMarin, Therachon and Ascendis, and grants from BioMarin. MBB has received consulting fees from and grants from BioMarin, Ascendis, Therachon, QED, and Alexion; and grants from BioMarin, Ascendis, Therachon, QED, Medlife, SOBI, and Shire. KKW has received consulting fees from BioMarin and Sanofi–Genzyme, and grants from BioMarin, Ultragenyx, and Ascendis.

#### Data sharing

The de-identified individual participant data that underlie the results reported in this Article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents might be available on request. Investigators will be able to request access to these data and supporting documents via a website beginning at 6 months and ending 2 years after publication. Data associated with any ongoing development programme will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at the BioMarin website to determine whether access will be given, contingent on execution of a data access agreement with BioMarin Pharmaceutical.

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For data access requests see  
[www.BioMarin.com](http://www.BioMarin.com)



## BRIEF COMMUNICATION

## Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

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**PURPOSE:** Achondroplasia is caused by pathogenic variants in the fibroblast growth factor receptor 3 gene that lead to impaired endochondral ossification. Vosoritide, an analog of C-type natriuretic peptide, stimulates endochondral bone growth and is in development for the treatment of achondroplasia. This phase 3 extension study was conducted to document the efficacy and safety of continuous, daily vosoritide treatment in children with achondroplasia, and the two-year results are reported.

**METHODS:** After completing at least six months of a baseline observational growth study, and 52 weeks in a double-blind, placebo-controlled study, participants were eligible to continue treatment in an open-label extension study, where all participants received vosoritide at a dose of 15.0 µg/kg/day.

**RESULTS:** In children randomized to vosoritide, annualized growth velocity increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at week 104. In children who crossed over from placebo to vosoritide in the extension study, annualized growth velocity increased from 3.81 cm/year at week 52 to 5.43 cm/year at week 104. No new adverse effects of vosoritide were detected.

**CONCLUSION:** Vosoritide treatment has safe and persistent growth-promoting effects in children with achondroplasia treated daily for two years.

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## INTRODUCTION

Achondroplasia is the most common form of disproportionate short stature in humans, caused by a common pathogenic variant in the fibroblast growth factor receptor 3 gene that confers a gain of function [1, 2]. People with achondroplasia experience significant medical and functional complications over their lifespan [2]. There are currently no approved precision therapies that target the underlying molecular etiology of this condition. Vosoritide, a modified C-type natriuretic peptide, stimulates endochondral ossification and is in clinical development to evaluate its safety and efficacy for the treatment of individuals with achondroplasia [3–5].

Studies in achondroplasia mouse models showed that subcutaneous administration of vosoritide increased long-bone and craniofacial growth [3, 4]. These data led to a growth study (to establish baseline growth over at least 6 months) and a

phase 2, open-label study in children aged 5 to <14 years with achondroplasia [5]. The safety and efficacy data from this study supported further clinical development of vosoritide at a dose of 15.0-µg-per-kilogram-per-day in children with achondroplasia in pivotal, randomized controlled studies. This phase 3 study was a 52-week, randomized, double-blind, placebo-controlled design, and conducted in 121 children with achondroplasia aged 5 to <18 years. Eligible children were randomized 1:1 to treatment with vosoritide or an identical matching placebo [6]. The mean difference in annualized growth velocity between participants in the vosoritide group and placebo group was 1.57 cm per year in favor of vosoritide (95% CI: [1.22, 1.93], two-sided *p* value <0.0001) [6]. In total, 119 participants experienced at least one adverse event; 59 in the vosoritide group (98.3%), and 60 in the placebo group (98.4%) [6].

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We report here an update from the phase 3 open-label extension study to document the efficacy and safety of up to two years of vosoritide treatment in children with achondroplasia.

## MATERIALS AND METHODS

Having completed at least six months of a baseline observational growth study (study 111-901; ClinicalTrials.gov number, NCT01603095), and 52 weeks in a double-blind, placebo-controlled, phase 3 study (study 111-301; EudraCT number, 2015-003836-11), children were then eligible to continue treatment in an open-label extension study (study 111-302; ClinicalTrials.gov number, NCT03424018).

In the placebo-controlled trial, children aged 5 to <18 years were randomized 1:1 to receive either vosoritide 15.0 µg/kg or placebo, for the duration of the 52-week treatment period administered by daily subcutaneous injections in their homes by trained caregivers. The dosing schedule was a single, daily subcutaneous injection given seven days a week, with regular injection site rotation. The clinical diagnosis of achondroplasia was confirmed by genetic testing. Children with radiographic evidence of closed growth plates, planned bone surgery, severe untreated sleep apnea, and other medical conditions or treatments known to impact growth were excluded. Written informed consent from a parent or legal guardian of each subject was obtained, and assent was obtained from the subject, if appropriate, prior to enrollment.

After completion of the placebo-controlled study, 119 children ( $n = 58$  from the active arm and  $n = 61$  from the placebo arm) were enrolled into the extension study, where all participants received vosoritide at a dose of 15.0 µg/kg/day. The data cut for this analysis occurred on 2 November 2020 when all ongoing participants had completed one year of follow up in the open-label extension study, which corresponds to two years on treatment for children originally randomized to vosoritide and one year on treatment for children who crossed over to vosoritide from placebo. Fifty-eight participants originally randomized to vosoritide continued vosoritide in the extension study. By week 104,  $n = 44$  participants had standing height assessments available to determine six-month interval annualized

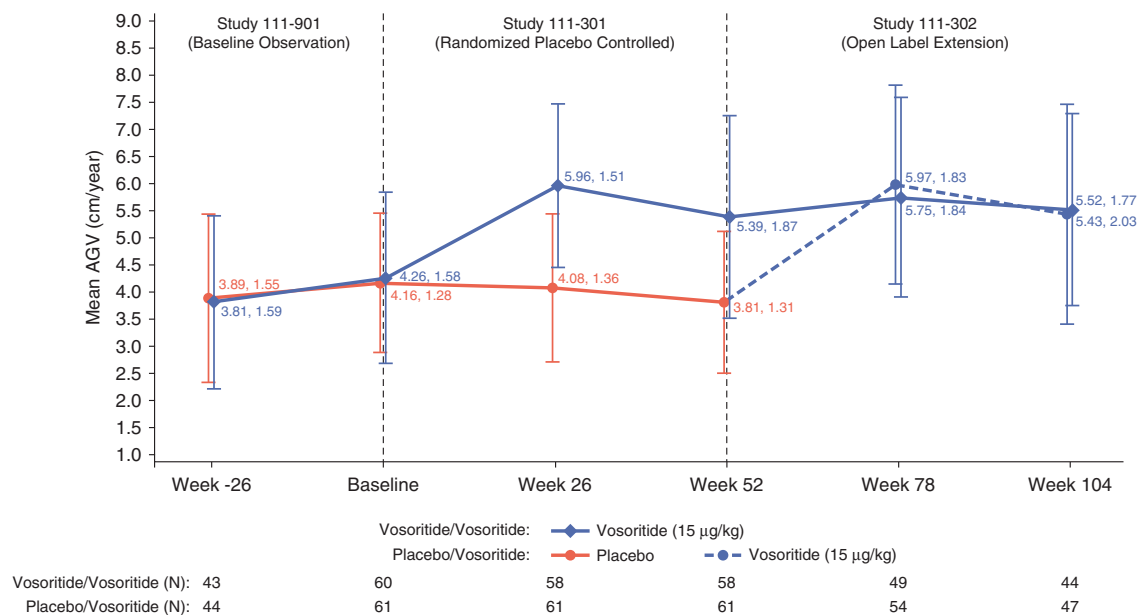
growth velocity at the two year analysis time point. Sixty-one participants crossed over from placebo to vosoritide in the extension study and  $n = 47$  had standing height assessments available to determine the six-month interval annualized growth velocity at the 2-year analysis time point. The cause of the missing data is principally due to disruptions to study visits due to the COVID-19 pandemic, where many site visits were replaced by virtual visits.

Descriptive summary plots for six-month interval annualized growth velocity are provided for the total of 121 children randomized to the placebo-controlled study using all available data from the baseline observational, randomized placebo-controlled and extension studies. A total of six six-month interval mean annualized growth velocity assessments were derived from standing height measurements commencing -52 weeks prior to randomization into the placebo-controlled study and concluding 104 weeks post randomization. The same summary plot was also produced where missing height data was imputed. Imputation for discontinued children was conducted as for the primary analyses of the randomized study by applying the baseline (pretreatment) annualized growth velocity to the last available height assessment. Linear interpolation was applied for the children who had missed the assessment but in whom an assessment at a later time point was available.

Standing height was converted to an age-appropriate and sex-appropriate Z-score by comparison with Centers for Disease Control and Prevention reference standards [7]. The upper-to-lower body segment ratio was calculated as the ratio between sitting height and standing height minus sitting height. Safety was evaluated by the incidence of adverse and serious adverse events.

## RESULTS

The annualized growth velocity was assessed overtime across the three studies over six-month intervals ([-12,-6 months], [-6,0 months], [0,6 months], [6,12 months], [12,18 months], and [18,24 months]) and included all children randomized into the placebo-controlled study (Fig. 1). The growth of participants



**Fig. 1** Line plot of mean annualized growth velocity shown in 6-month intervals starting in the baseline observation study and continuing through the randomized placebo-controlled study for 52 weeks and then into the extension study for a total of 104 weeks, displayed by treatment arm derived from observed data. Numbers at each time point reflect mean annualized growth velocity in cm/year and the standard deviation. Orange and dotted blue lines represent annualized growth velocity for participants randomized to the placebo study treatment arm and the solid blue lines represent annualized growth velocity for participants in the vosoritide study treatment arm. After 52 weeks and completion of the phase 3 study, 119 children were enrolled into the extension study, where all participants received vosoritide at a dose of 15 µg/kg/day. Fifty-eight participants originally randomized to vosoritide continued vosoritide in the extension study. By week 104,  $n = 44$  participants had standing height assessments available to determine six-month interval annualized growth velocity at the two-year analysis time point. Sixty-one participants crossed over from placebo to vosoritide in the extension study and  $n = 47$  had standing height assessments available to determine the six-month interval annualized growth velocity at the 2-year analysis time point. The cause of the missing data is disruptions to study visits due to the COVID-19 pandemic, where many site visits were replaced by virtual visits.

during the baseline observational study was consistent between both placebo and vosoritide treatment groups. Baseline mean annualized growth velocity (SD) in children randomized to treatment with vosoritide was 3.81 (1.59) cm/year at -6 months and 4.26 (1.58) cm/year at baseline immediately before entering into the randomized study. In children randomized to treatment with placebo, the annualized growth velocity was 3.89 (1.55) cm/year at -6 months and 4.16 (1.28) cm/year at baseline.

In the placebo-controlled study, children randomized to treatment with vosoritide increased annualized growth velocity to 5.96 (1.51) cm/year at 26 weeks and 5.39 (1.87) cm/year at 52 weeks. In children randomized to placebo the annualized growth velocity was 4.08 (1.36) cm/year at 26 weeks and 3.81 (1.31) cm/year at 52 weeks.

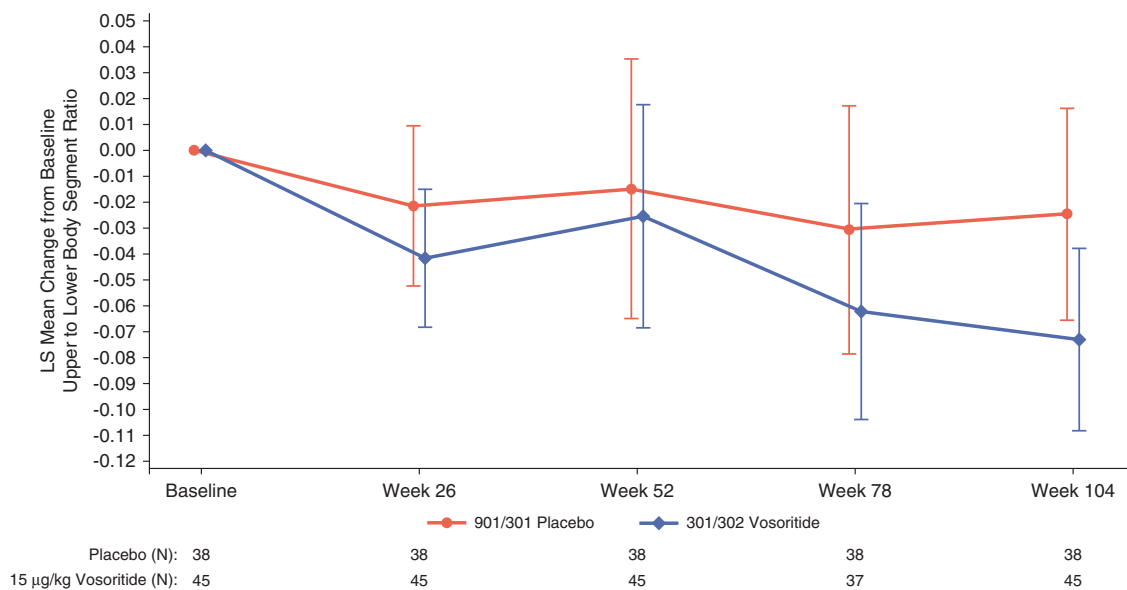
The improvement in annualized growth velocity observed in children treated with vosoritide in the randomized placebo-controlled study was maintained in the open-label extension study with an annualized growth velocity of 5.75 (1.84) cm/year at week 78 and 5.52 (1.77) cm/year at week 104. Annualized growth velocity also increased to 5.97 (1.83) cm/year at week 78 and 5.43 (2.03) cm/year at week 104 in children who crossed over from placebo to vosoritide in the open-label extension study, resembling the initial treatment effect observed in the vosoritide arm at the start of treatment in the randomized study. Sensitivity analyses where all missing data were imputed were consistent with the summary plot on all observed data and are available in the supplementary information (Fig. S1). Spaghetti plots of standing height by age for individual participants are available in the supplementary information (Figs. S2–S5).

Comparative analyses were also conducted to assess the height gain for all participants randomized to the active arm after two years on active treatment with a height assessment at week 104

( $n = 52$ ) versus the participants in the placebo arm with two years of untreated follow up considering the placebo period and an additional year from the observational study prior to start of the randomized controlled study ( $n = 38$ ). By directly comparing the treated group to the untreated group, the observed change in height was similar in the first year of treatment, 1.73 cm, as in the second year of treatment, 1.79 cm. The additional height gain over the two-year treatment period was 3.52 cm more than the untreated children. Comparative analyses at two years were performed using the same analysis of covariance (ANCOVA) model, which adjusted for covariates, as prespecified for the primary and key secondary analyses of the randomized placebo-controlled study, the LSmean difference (95% CI) was 3.34 cm (2.76, 3.93). Similarly, comparative analyses were also conducted to assess height Z-score and upper-to-lower body segment ratio. Using the same ANCOVA model, the difference in LSmean change in height Z-score (95% CI) was +0.44 (0.25, 0.63) at week 104 and the difference in LSmean change from baseline in upper-to-lower body segment ratio (95% CI) was -0.05 (-0.09, -0.01) at week 104 representing a greater decrease in the body ratio in the vosoritide treated versus the untreated participants (Fig. 2, Table S1).

No new adverse effects of vosoritide treatment at 15 µg/kg/day were detected with two years of continuous daily, subcutaneous treatment. Most adverse events were mild and no serious adverse events were attributed to vosoritide. The most common adverse event remains mild and transient injection site reactions.

Bone age was assessed with the Greulich and Pyle method using X-rays of the left hand and wrist. Bone age continued to progress normally in all children over the 104-week observation period. After one year of treatment, mean (SD) change from baseline in bone age considering assessments for both placebo



**Fig. 2** Line plot showing analysis of covariance (ANCOVA) LSmean change from baseline with 95% confidence intervals (CI) for upper-to-lower body segment ratio in 6-month intervals for a total of 24 months and displayed by treatment arm. Separate ANCOVA models provide the LSmean change from baseline at each time point for the participants who had completed the 2-year follow up. Orange lines represent change from baseline in upper-to-lower body segment ratio for participants randomized to the baseline observation study and the placebo study treatment arm and the solid blue lines represent change from baseline in upper-to-lower body segment ratio for participants in the vosoritide study treatment arm. Comparative analyses were conducted for all participants randomized to the active arm after two years on active treatment with an assessment at month 24 ( $n = 45$ ) versus the participants in the placebo arm with two years of untreated follow up considering the one year placebo period and an additional year from the observational study prior to start of the randomized controlled study ( $n = 38$ ). By directly comparing the treated group to the untreated group, comparative analyses at two years were performed using the same ANCOVA model, which adjusted for covariates, as prespecified for the primary and key secondary analyses of the randomized placebo-controlled study, the LSmean change from baseline in upper-to-lower body segment ratio (95% CI) was -0.05 (-0.09, -0.01) at week 104 representing a greater decrease in the body ratio in the vosoritide treated versus the untreated participants.

and active arms was 1.10 years (0.89) for males ( $n = 46$ ) and 1.01 years (0.94) for females ( $n = 41$ ). The mean (SD) change from baseline in bone age after 2 years was 2.58 (1.33) years in males ( $n = 18$ ) and 1.58 (1.42) years in females ( $n = 18$ ).

## DISCUSSION

The effect of daily subcutaneous administration of vosoritide on growth as measured through annualized growth velocity and height Z-score was maintained for up to two years in children with achondroplasia aged 5 to 18 years, with an improvement in body proportions. There were no serious treatment-related adverse effects and vosoritide was well tolerated.

These data are consistent with those observed in the phase 2 and 3 clinical trials of vosoritide, where the increase in annualized growth velocity approached that of average-statured children of a similar age [5, 6]. They provide further, robust clinical evidence that vosoritide is an effective precision therapy for children aged 5 to 18 years with achondroplasia [5, 6]. No adverse effects on bone maturation have been observed in these trials. This, combined with the improvements in body segment proportionality, suggests that longer periods of treatment with vosoritide commenced at an earlier age might result in sustained enhancement of skeletal growth, with clinically and functionally beneficial consequences. Due to the inherent variability of growth and the lesser magnitude of the pubertal growth spurt in children with achondroplasia, these long-term effects will only be known once these children reach final adult height [2].

The extension study reported here will also provide answers to whether vosoritide treatment will decrease the medical complications associated with achondroplasia, and improve functional outcomes. The study will collect data on other health measures, such as quality of life and incidence of expected complications, and these will be compared with registry data from untreated age-matched children with achondroplasia. This study will have the ability to detect if there are any long-term adverse effects of vosoritide therapy, and the effect of this therapy on pubertal growth acceleration in children with achondroplasia.

Other, ongoing clinical trials (ClinicalTrials.gov numbers NCT03583697, and NCT04554940) of vosoritide will investigate its safety and efficacy in children with achondroplasia aged 3 months to 60 months, and in infants at risk of requiring cervicomedullary decompression surgery [8]. These trials will provide further insights into the long-term treatment effects on skeletal growth, body proportions, and functionality, as well as how treatment might ameliorate the most significant medical complications in achondroplasia, specifically foramen magnum stenosis with brainstem compression and sudden death.

Overall, vosoritide treatment has safe and persistent growth-promoting effects in children with achondroplasia, and offers a precision therapy for patients impacted by this condition.

## DATA AVAILABILITY

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request.

Investigators will be able to request access to these data and supporting documents via a website ([www.BioMarin.com](http://www.BioMarin.com)) beginning six months and ending two years after publication. Data associated with any ongoing development program will be made available within six months after approval of the relevant product.

Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at [www.BioMarin.com](http://www.BioMarin.com) to determine if access will

be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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## AUTHOR CONTRIBUTIONS

Conceptualization: R.S., A.H.-L., J.D. Data curation: R.S., A.H.-L., J.D., D.P., K.J., E.F. Formal Analysis: A.H.-L. Funding acquisition: J.D. Investigation: R.S., L.T., M.I., W.R.W., C.A.B., J.H.-F., R.U.F., P.H., F.R., M.B.B., L.E.P., I.G., K.M., J.C., D.H., K.O., Y.A., P.A., Y.K., N.Y., K.W., H.M.S., A.L.-G., F.L.-G., H.M., D.B. Methodology: R.S., E.F., J.D. Project administration: D.P., E.F., K.J. Resources: J.D. Software: A.H.-L. Supervision: R.S., E.F., J.D. Validation: R.S., E.F., A.H.-L., J.D. Visualization: R.S., J.D. Writing—original draft: R.S., J.D. Writing—review & editing: R.S., L.T., M.I., W.R.W., C.A.B., J.H.-F., R.U.F., P.H., F.R., M.B.B., L.E.P., I.G., K.M., J.C., D.H., K.O., Y.A., P.A., Y.K., N.Y., K.W., H.M.S., A.L.-G., F.L.-G., H.M., D.B., A.H.-L., J.D.

## COMPETING INTERESTS

All authors were investigators in this clinical trial except for D.P., K.J., E.F., A.H.L. and J.D., who are employees of the funder (BioMarin). R.S., L.T., F.R. and K.M. have received consulting fees and grants from BioMarin. M.I. and W.W. have received consulting fees from BioMarin. J.C. and D.B. have received grants from BioMarin. LP and PA have received honoraria from BioMarin. C.B. and P.H. have received consulting fees, honoraria and grants from BioMarin. J.H.F. has received consulting fees from BioMarin, Therachon AG and Ascendis, and grants from BioMarin. M.B. has received consulting fees from and grants from BioMarin, Ascendis, Therachon, QED and Alexion; and grants from BioMarin, Ascendis, Therachon, QED, Medlife, SOBI, and Shire. K.W. has received consulting fees from BioMarin and Sanofi/Genzyme, and grants from BioMarin, Ultragenyx, and Ascendis. The other authors declare no competing interests.

## ETHICS DECLARATION

This study received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC) with reference number HREC/37252. All other institutions represented in this paper received local IRB approval prior to enrollment of the first participant at their institute. Written, informed consent was

obtained from all parents/caregivers of enrolled participants as per protocol and IRB requirements.

### ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41436-021-01287-7>.

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## BRIEF REPORT

# Persistent growth-promoting effects of vosoritide in children with achondroplasia are accompanied by improvements in physical and social aspects of health-related quality of life

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### ABSTRACT

**Purpose:** Evaluate the impact of vosoritide on health-related quality of life in children with achondroplasia.

**Methods:** Participants received vosoritide (15 µg/kg/day) in an extension trial (NCT03424018) after having participated in a placebo-controlled trial (NCT03197766).

**Results:** The population comprised 119 participants (mean [SD] age 9.7 [2.6] years). Mean treatment duration was 4 (0.78) years. At year 3, the largest mean (SD) changes were observed in the Quality of Life of Short Stature Youth physical score (5.99 [19.41], caregiver reported; 6.32 [20.15], self-reported) and social score (2.85 [8.29] and 6.76 [22.64], respectively). Changes were greatest in participants with  $\geq 1$  SD increase in height z-score (physical: 11.36 [19.51], caregiver-reported [ $n = 38$ ]; 8.48 [21.83], self-reported [ $n = 28$ ]) (social: 5.84 [15.45] and 9.79 [22.80], respectively). To determine how domain scores may change with age in untreated persons, models were produced using observational/untreated-person data. A 1-year increase in age was associated with a change of 0.16 (SE, 0.55) and 0.16 (0.50), for caregiver-reported physical and social domain scores, respectively. Self-reported scores changed by 1.45 (0.71) and 1.92 (0.77), respectively.

**Conclusion:** These data suggest that after 3 years of treatment, vosoritide demonstrates a positive effect on physical and social functioning among children with achondroplasia, particularly in children with a more pronounced change in height z-score.

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## Introduction

Achondroplasia, the most prevalent form of disproportionate short-stature skeletal dysplasia, is present in approximately 1 in 25,000 live births.<sup>1,2</sup> It is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene (*FGFR3*).<sup>2,3</sup> Over-activation of *FGFR3* impairs endochondral ossification, leading to a characteristic pattern of skeletal features,<sup>1,2</sup> including disproportionate short stature and macrocephaly.<sup>1,4</sup> These bone growth and development abnormalities are associated with a high burden of functional impairment and potentially severe medical complications<sup>3,5,6</sup> and reduced quality of life, due in part to disproportionate short stature.<sup>7</sup>

Evidence from phase 2 and 3 clinical trials and extension studies demonstrates that vosoritide, a C-natriuretic peptide analog, increases annualized growth velocity after 1 year of treatment in children with achondroplasia<sup>8,9</sup> and that this improvement is maintained at 3 years.<sup>10</sup> Findings at 2 years indicate trends in improved upper-to-lower body segment proportions, with a least squares mean change from baseline in upper-to-lower body segment ratio of  $-0.05$  ( $-0.09$ ,  $-0.001$ ), representing a greater decrease in body ratio.<sup>11</sup> Vosoritide is well tolerated, with a mild adverse event profile in infants and children.<sup>11,12</sup> Vosoritide is approved for the treatment of children with achondroplasia and open epiphyses from birth in the United States, Japan, and Australia and from age  $\geq 4$  months in the European Union and  $\geq 6$  months in Brazil.

One key issue to address is whether children with achondroplasia derive health-related quality-of-life (HRQoL) benefits through the increased height and improved body proportionality achieved with vosoritide treatment. Such benefits take time to manifest, indicating the need to start treatment early so that children can achieve the maximum functional and HRQoL benefits from their increased stature and improved proportionality. The aim of these preliminary analyses was to investigate the effect of vosoritide on HRQoL in children with achondroplasia in an ongoing open-label extension study.

## Materials and Methods

A total of 121 children aged 5 years to  $<18$  years at screening, with a clinical diagnosis of achondroplasia confirmed by genetic testing, were eligible for enrollment in the 111-301 randomized placebo-controlled study (study 111-301; NCT03197766).<sup>8</sup> Of these, 119 were enrolled in the 111-302 open-label extension study (NCT03424018), in which all participants received daily subcutaneous injections of vosoritide at a dose of 15  $\mu\text{g}/\text{kg}$ . HRQoL data were collected in both studies. Race and ethnicity were determined for participating children at enrollment through specific questioning of parents or guardians by the investigators. Race and ethnicity data were not collected for

parents or guardians. The current analysis focuses on a data cutoff of February 25, 2023, at which time data collection was complete to year 3 for all participants (barring discontinuation), although for those participants randomized to vosoritide in 111-301 data were complete (barring discontinuation) up to 4 years. Baseline was defined as the assessment on the first day of vosoritide administration (in 111-301 or 302).

A secondary outcome in the 111-302 study was evaluation of change from baseline in HRQoL measured using the Quality of Life of Short Stature Youth (QoLISSY),<sup>13</sup> a multidimensional, participant- and caregiver-reported outcome measure developed to assess HRQoL in children with short stature and suitable for use in children with achondroplasia.<sup>14,15</sup> The Quality of Life of Short Stature Youth (QoLISSY) has a caregiver-report version (from age 4) and self-report version (from age 8) and comprises 3 core domains (physical, social, and emotional), which are summed and averaged to create the total score, and 5 additional domains (coping, belief, treatment, future, and effects on parents) (Supplemental Methods). Raw QoLISSY scores were transformed on a scale of 0 to 100, with higher values representing higher HRQoL. Children and/or their caregivers completed the QoLISSY at baseline and at 6-monthly intervals. Only the caregiver version was administered among all participants at baseline.

## Statistical analysis

These analyses are based on on-treatment data (up to 45 days posttreatment discontinuation). Data are presented as mean with standard deviation (SD) or standard error (SE) or as median (25th and 75th percentiles).

Descriptive summary statistics are provided for mean annual change from baseline for each of the domains and for QoLISSY total score for caregiver- and self-reported questionnaires for all children with an assessment at baseline and up to the week 234 (4.5 years). Subgroup analyses for all domains (except treatment, which was not used in this study) were conducted at year 3 in children with  $<1$  SD change in achondroplasia height  $z$ -score at this time point and in those with  $\geq 1$  SD change (whereby an increase of change in achondroplasia height  $z$ -score indicates an improvement).<sup>16</sup> Similarly, subgroup analyses for participants with a change in upper-to-lower body ratio of  $<-0.2$  (which indicates a greater improvement) and in those with a change of  $\geq -0.2$  at year 3 were conducted for all domains (except treatment, which was not used in this study).

To facilitate the interpretation of the results in the treated population, in which the treatment effect would be confounded with increase in age, models were produced to determine the effect of increase in age using observational data from completed BioMarin (BMN) 111-901 (ClinicalTrials.gov number, NCT01603095)<sup>17</sup> and placebo data from BMN 111-301 (ClinicalTrials.gov number, NCT03197766).<sup>8</sup> Mixed models were fitted for each domain

score, including fixed effects for age and sex and random participant effects. Each model provided an estimate for the change in a score associated with a 1-year increase in age for each domain score in the untreated setting.<sup>8,17</sup>

Statistical analyses were performed with SAS version 9.4 (SAS Institute). ProPhase Labs, Inc were contracted by BioMarin to collect and score the QoLISSY data.

## Results

Mean (SD) age at baseline (start of active vosoritide treatment) of the 119 participants receiving vosoritide was 9.2 (2.6), 47.1% were female and 71.4% were white (Table 1). Twenty-nine participants (24.4%) had a baseline Tanner score >I. Mean (SD) height z-score—referenced to average stature children using data from Centers for Disease Control and Prevention—was  $-5.12$  (1.09), and upper-to-lower body ratio was 1.98 (0.19) (median 1.99, 25th, 75th percentile 1.88, 2.11). Mean (SD) baseline caregiver-reported QoLISSY total score was 57.46 (19.03) ( $n = 113$ ), and self-reported total score was 64.50 (18.44) ( $n = 73$ ) (Supplemental Table 1). At the time of the data cut (February 25, 2023), data collection was complete to year 3 for all participants. Some participants had up to 6 years of follow-up; however, summary tables included only up to 4.5 years of follow-up because the data were too sparse to summarize after this point. Mean (SD) treatment duration was 4 (0.78) years.

QoLISSY total score at year 3 increased relative to baseline, as reported by caregivers (mean change 3.25 [15.48]) and participants (5.43 [17.74]) (Supplemental Table 1), and to a greater extent, in the subgroup (47/113; 42%), with  $\geq 1$  SD increase in achondroplasia height z-score (6.94 [13.13] for caregiver reported [ $n = 38$ ] and 8.31 [19.75] for self-reported [ $n = 27$ ]) (Figure 1, Supplemental Table 2). Among participants with a decrease change in upper-to-lower body ratio of  $< -0.2$ , mean changes in total score were 5.58 (13.00) for caregiver-reported score ( $n = 19$ ) and 4.93 (24.82) for self-reported ( $n = 7$ ) score (Supplemental Table 3).

The greatest changes over time were observed for QoLISSY physical and social scores (Supplemental Tables 3-9). Specifically, mean changes from baseline for QoLISSY physical score at 3 years were 5.99 (19.41) for caregiver reported and 6.32 (20.15) for self-reported scores (Supplemental Table 4). These changes were driven primarily by participants with a  $\geq 1$  SD increase in achondroplasia height z-score, in whom the mean changes were 11.36 (19.51) for caregiver-reported ( $n = 38$ ) and 8.48 (21.83) for self-reported ( $n = 28$ ) scores (Supplemental Table 5). Summaries are provided for participants with a change in upper-to-lower body ratio of  $< -0.2$ , for which mean changes were 12.67 (16.42) for caregiver reported ( $n = 19$ ) and 10.71 (29.55) for self-reported ( $n = 7$ ) scores (Supplemental Table 6). Mixed models for the untreated

**Table 1** Participant characteristics

Characteristic	Vosoritide Treated ( $n = 119$ )
Age at first assessment (years)	
Mean (SD)	9.2 (2.6)
Median (Min, Max)	9.22 (5.1, 15.9)
Age subgroup (%)	
$\geq 5$ to $< 8$ years	46 (38.7)
$\geq 8$ to $< 11$ years	37 (31.1)
$\geq 11$ to $< 15$ years	35 (29.4)
$\geq 15$ to $< 18$ years	1 (0.8)
Female sex (%)	56 (47.1)
Race (%)	
Asian	21 (17.6)
Black or African American	5 (4.2)
White	85 (71.4)

Race and ethnicity were determined for participating children at enrollment through specific questioning of parents or guardians by the investigators. Race and ethnicity data were not collected for parents or guardians.

QoLISSY, Quality of Life of Short Stature Youth.

achondroplasia population provided an estimated annual slope [mean (SE)] for the physical domain score of 0.16 (0.55) for caregiver-reported outcomes and 1.45 (0.77) for self-reported outcomes (Supplemental Table 10).

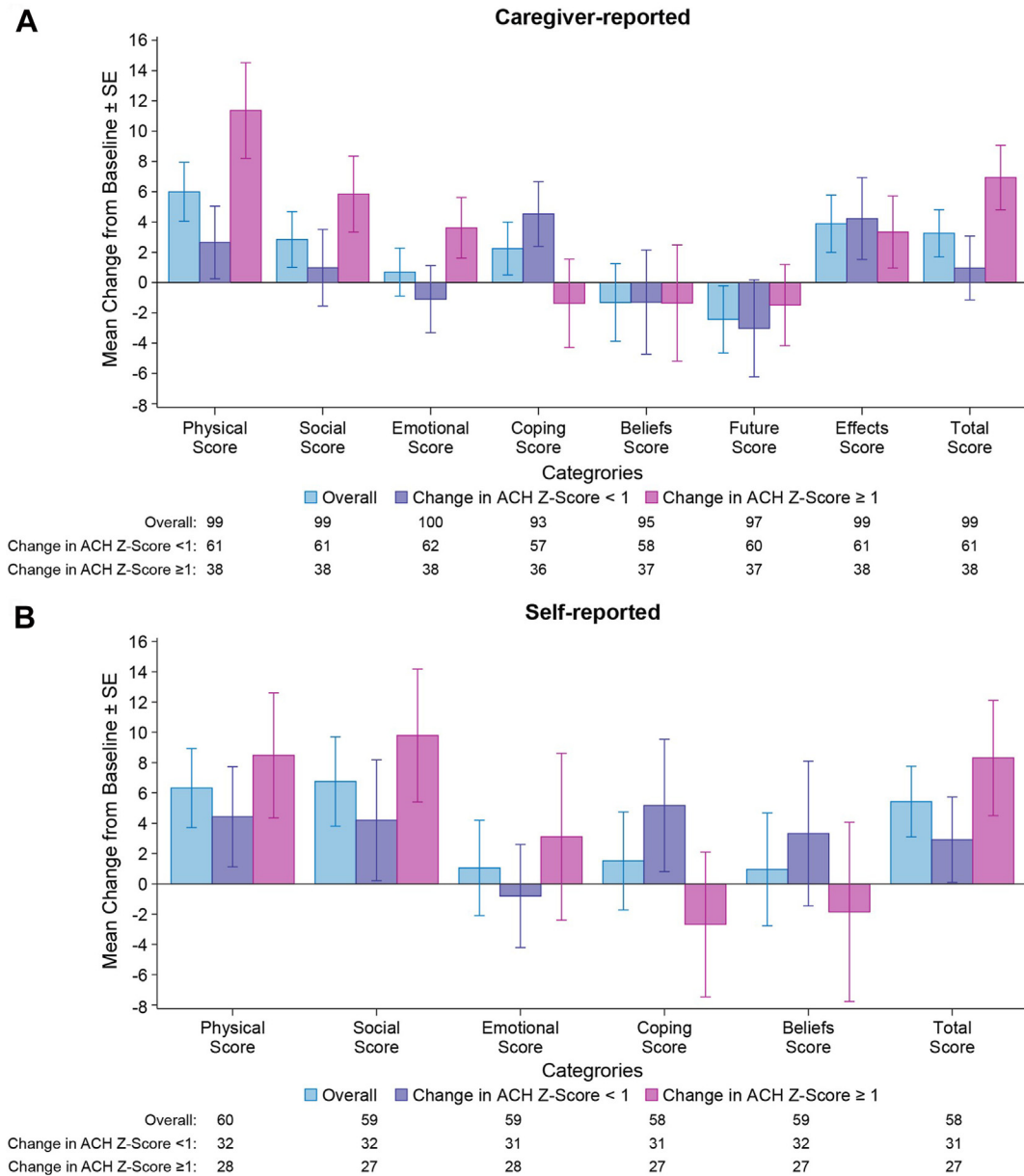
Similar changes from baseline were observed for QoLISSY social score (Supplemental Table 7). Mean changes from baseline for QoLISSY social score at 3 years were 2.85 (18.29) for caregiver-reported score and 6.76 (22.64) for self-reported score. These changes were driven primarily by participants with a  $\geq 1$  SD increase in achondroplasia height z-score, in whom the mean changes were 5.84 (15.45) (caregiver reported;  $n = 38$ ) and 9.79 (22.80) (self-reported;  $n = 27$ ) (Supplemental Table 8). Caregiver-reported social scores improved in children with a  $< -0.2$  change in their upper-to-lower body ratio (1.88 [17.24];  $n = 19$ ), whereas self-reported social score did not show improvement ( $-0.77$  [35.60];  $n = 7$ ) (Supplemental Table 9). Mixed models for the untreated achondroplasia population provided an estimated annual slope [mean (SE)] for the social domain score of 0.16 (0.50) for caregiver-reported outcomes and 1.92 (0.77) for self-reported outcomes (Supplemental Table 10).

The results for the other domain scores did not demonstrate such clear and consistent trends at the 3-year time point (Supplemental Tables 11-25) as shown in the physical scores.

No serious treatment-related adverse effects were reported and vosoritide was well tolerated.<sup>8,11</sup>

## Discussion

In children with achondroplasia aged 5 to 15 years enrolled in this open-label extension study, 3 years of daily vosoritide treatment resulted in consistent improvements in



**Figure 1** Mean change from baseline in Quality of Life of Short Stature Youth (QoLISSY) at year 3, overall and by change in achondroplasia height z-score (treated participants). \*Effects on parents.

QoLISSY physical and generally for the social domain scores. This was broadly consistent between self-reported and caregiver-reported scores. Changes in the scores for the caregiver assessments at year 3 for treated participants were greater than the expected changes in the untreated setting, as determined from models produced from a similar untreated achondroplasia population.<sup>8,11</sup> The changes generally correlated with greater increases in height in participants with a  $\geq 1$  increase in their achondroplasia height z-score. By contrast, for the assessments on the body proportion subgroup, the results were unclear. The sample size was small ( $N = 7$ ), and further follow-up is warranted for these analyses.

These preliminary results suggest a positive treatment effect of vosoritide on HRQoL in children with achondroplasia,

as assessed by the QoLISSY physical and social domains. It is unsurprising that changes in the physical domain have emerged because these items assess concepts most closely relate to physical changes observed because of treatment (height gain and improved proportionality). Improvements in social domain scores also reflect the downstream benefits of treatment, although individual and environmental confounders could affect the rate of change over time. Remaining domains (emotional, coping, belief, future, and effects on parents) assess concepts disproportionately affected by confounding factors (eg, psychological and environmental, caregiver perception of their own well-being rather than the child's); therefore, marked improvements in these domains were not expected within the context of a trial as a result of treatment. The data suggest that those who had the largest

improvement in their height deficit experienced the greatest treatment impact to date, as reflected by their (and their caregiver's) QoLISSY physical scores. In the cross-sectional observational Lifetime impact of achondroplasia study in Europe study,<sup>6</sup> height z-score was a key factor deemed to be meaningfully associated with HRQoL. Consistent with the findings reported here and in other studies,<sup>18,19</sup> children in the Lifetime impact of achondroplasia study in Europe study scored their own HRQoL higher than their parents across most domains.

The results from this study suggest that there are quality-of-life benefits related to improved height deficit observed in children with achondroplasia treated with vosoritide, which take time to accumulate.<sup>11</sup> These findings support the argument for early initiation of treatment, in line with current global approvals, so that children can achieve the maximum functional and HRQoL benefits from their increased stature and improved proportionality. Early initiation of treatment might also lead to beneficial effects on other aspects of achondroplasia, such as foramen magnum stenosis, a major risk factor for sudden death in children under the age of 5.<sup>5,6</sup> The impact of these changes, clinically and in terms of HRQoL, will be investigated in ongoing studies (NCT03989947 and NCT04554940<sup>20</sup>).

These are preliminary analyses, and further follow-up is required to assess these preliminary trends, particularly for the subgroups for which the sample sizes were small. The study is limited because of the absence of a control group; however, the results from the models help to interpret the results and draw conclusions on the potential effect of vosoritide. It is also acknowledged that, for some analyses, the sample sizes were small, particularly for subanalyses stratified by change in upper-to-lower body ratio. However, these are preliminary analyses to identify potential trends, and we would expect these subgroups to increase in size in large data cuts. In addition, some participants were pubertal at initiation of treatment with vosoritide and therefore less likely to see improvements in height deficit and HRQoL than younger children. In spite of this, we believe the breadth of the analyses described here offer important insights into the impact of vosoritide on different aspects of HRQoL that were previously not available. Another potential limitation of this study is that participants and their caregivers all chose to receive long-term treatment with vosoritide, which could be a source of confirmation bias.

Self-reported data in these analyses were limited to participants aged  $\geq 8$  years at the start of treatment. Further work is ongoing to better understand the clinical meaningfulness of these improvements.

## Conclusions

The results from this study suggest that 3 years of treatment with vosoritide may translate into improvements in the HRQoL of children with achondroplasia, as shown by increased caregiver-reported and self-reported QoLISSY

scores over time. Changes were most marked in physical and social domain scores, with the most pronounced effects reported in participants who had more marked improvements in height deficit and reductions in body proportionality for the physical domain. This study adds to the growing body of evidence that the established positive effects of vosoritide treatment on growth velocity, height, and body proportionality in children with achondroplasia may translate into positive effects on participants' functioning and HRQoL. With the accumulation of longer-term follow-up data, the cumulative effects of vosoritide on other medical, functional, and psychosocial challenges experienced by children with achondroplasia will become clearer.

## Data Availability

The deidentified individual participant data that underlie the results reported in this article (including text, tables, figures, and supplemental material) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a website (BioMarin.com) beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at [www.BioMarin.com](http://www.BioMarin.com) to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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The study was funded by BioMarin Pharmaceutical Inc.

## Author Contributions

Conceptualization: R.S., A.H.-L., J.D.; Data Curation: R.S., R.R., A.H.-L., J.D., K.J., E.F.; Formal Analysis: R.R., A.H.-L.; Funding Acquisition: J.D.; Investigation: R.S., M.I., W.R.W., C.A.B., J.E.H.-F., P.H., C.E.P., T.K., P.A., A.L.-G.; Methodology: R.S., A.L., I.S., J.D.; Project Administration: A.L., I.S.; Resources: J.D.; Software: A.H.-L.; Supervision: R.S., A.L., I.S., J.D.; Validation: R.S., A.L., I.S., A.H.-L., J.D.; Visualization: R.S., J.D.; Writing-original draft: R.S., J.D.; Writing-review and editing: R.S., M.I., W.R.W., C.A.B., J.E.H.-F., P.H., C.E.P., T.K., P.A., A.L.-G., R.R., A.L., I.S., A.H.-L., J.D.

## Ethics Declaration

This study received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC) with reference number HREC/37252. All other institutions represented in this paper received local institutional review board approval before enrollment of the first participant at their institute. Written, informed consent was obtained from all parents/caregivers of enrolled participants as per protocol and institutional review board requirements.

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## Conflict of Interest

All authors were investigators in this clinical trial except for Richard Rowell, Andrea Low, Ian Sabir, Alice Huntsman-Labed, and Jonathan Day, who are employees of the funder (BioMarin). Antonio Leiva-Gea has received consulting fees from BioMarin, has participated as a clinical trial investigator for BioMarin and QED Therapeutics, has received speaker fees from BioMarin, MBA, and EAF, and has received travel support from BioMarin and MBA. Carlos A. Bacino has received consulting fees from BioMarin and has participated as clinical trial investigator for Roche, BioMarin and Ascendis. Carlos E. Prada has received consulting fees from BioMarin, Sanofi, and Takeda, has participated as a clinical trial investigator for BioMarin, Sanofi, Hemoshear, and Prevail, and has received speaker payments from Sanofi. Julie E. Hoover-Fong has received consulting fees from BioMarin, Ascendis, QED Therapeutics, Innoskel, and Tyra, has received research grants from Alexion, has participated as a clinical trial investigator for BioMarin, QED Therapeutics, and Pfizer/Therachon, has received speaker fees from Medscape, and has received travel support from BioMarin, QED Therapeutics, and Tyra. Klaus Mohnike has received consulting payments from BioMarin, QED Therapeutics and Novo Nordisk, has participated as a clinical trial investigator for BioMarin, and has received speaker fees and travel support from BioMarin and Novo Nordisk. Lynda E. Polgreen has received consulting fees from BioMarin, Lysogene, and Denali, has participated as a clinical trial investigator for BioMarin, Pfizer, and Takeda, and has received travel support from BioMarin. Melita Irving has received consulting fees from BioMarin, QED Therapeutics/Bridge Bio, Ascendis, Sanofi, and Tyra, has participated as a clinical trial investigator for BioMarin, QED Therapeutics/Bridge

Bio, and Ascendis, has received speaker fees from BioMarin, QED Therapeutics/Bridge Bio, Ascendis, Ipsen, and Sandoz, and has received travel support from BioMarin, QED Therapeutics/Bridge Bio, and Ascendis. Paul Harmatz has received consultancy fees from Grace Science, Rallybio, Neurogene, Novel Pharma, and Orchard Therapeutics, has received speaker fees, travel support, and travel grants from BioMarin, has received research funding from Adrenas, Amicus, Ascendis, ASPA, Azafaros, BioMarin, Calcilytics, Denali, Homology, JCR Pharmaceuticals, Orphazyme, QED Therapeutics, RegenXbio, Sangamo, Takeda, Idorsia, Prevail, and Allievex, and has participated as a clinical trial investigator for BioMarin. Ravi Savarirayan has received consulting fees and travel support from BioMarin, QED Therapeutics, and Ascendis, and has participated as a clinical trial investigator for BioMarin, QED Therapeutics, Ascendis, and Sanofi. Takuo Kubota has received speaker payments from BioMarin and Novo Nordisk and research grants from Eli Lilly. William R. Wilcox has received consulting fees from BioMarin and has participated as a clinical trial investigator for BioMarin. All other authors declare no conflicts of interest.

## Additional Information

The online version of this article (<https://doi.org/10.1016/j.gim.2024.101274>) contains supplemental material, which is available to authorized users.

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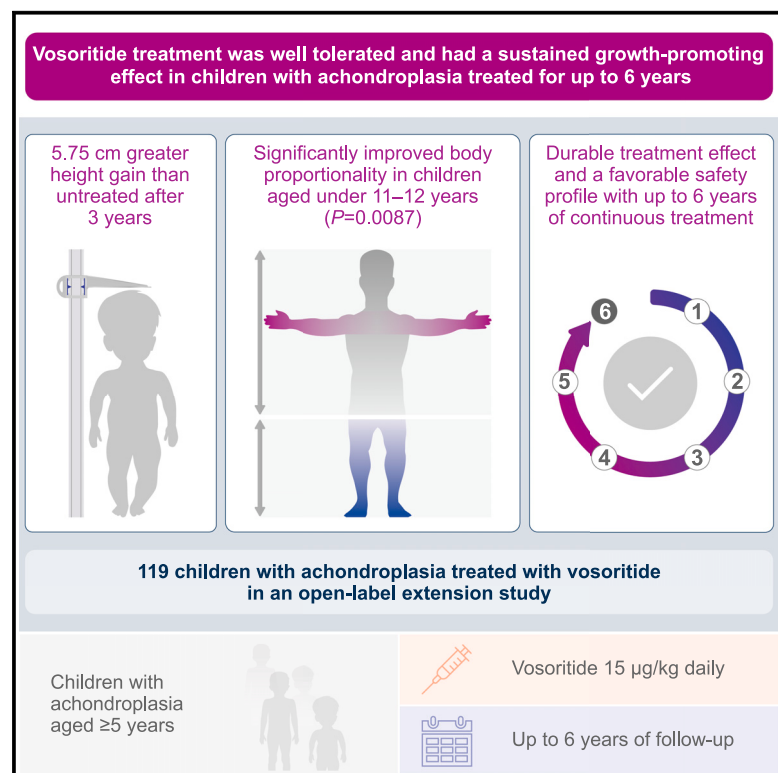
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# Sustained growth-promoting effects of vosoritide in children with achondroplasia from an ongoing phase 3 extension study

## Graphical abstract



## Highlights

- Vosoritide led to a height gain of 5.75 cm more than untreated children at 3 years
- Vosoritide significantly improved upper-to-lower body segment ratio at 3 years
- Vosoritide had a favorable safety profile with continuous treatment for up to 6 years

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## In brief

This long-term extension study of vosoritide in 119 children with achondroplasia showed durability of treatment effect over 6 years and significant improvement of body proportionality at 3 years of treatment as compared to an untreated cohort. No new harms were identified and no deaths reported.

## Translation to Patients



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Article

# Sustained growth-promoting effects of vosoritide in children with achondroplasia from an ongoing phase 3 extension study

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**CONTEXT AND SIGNIFICANCE** Achondroplasia is a genetic skeletal disorder characterized by a short-limbed, short stature and a variety of consequent medical, functional, and psychosocial challenges over the lifespan in affected individuals. The only currently approved medication for children with achondroplasia is vosoritide, a C-type natriuretic peptide analog that has been shown to increase annual growth velocity in these children. This study looked at the long-term efficacy and safety of vosoritide in 119 children enrolled in an open-label extension study that followed the pivotal phase 3 trial. It reports sustained growth-promoting effects of vosoritide in these children with up to 6 years of treatment duration and improvement of body proportionality in younger children (aged <11–12 years). No new harms of treatment were identified.

## SUMMARY

**Background:** Vosoritide is a C-type natriuretic peptide analog that addresses an underlying pathway causing reduced bone growth in achondroplasia. Understanding the vosoritide treatment effect requires evaluation over an extended duration and comparison with outcomes in untreated children.

**Methods:** After completing  $\geq 6$  months of a baseline observational growth study and 52 weeks in a double-blind, placebo-controlled study (ClinicalTrials.gov: NCT03197766), participants were eligible to continue treatment in an open-label extension (ClinicalTrials.gov: NCT03424018) wherein all received 15  $\mu\text{g}/\text{kg}$  vosoritide daily. Data from the CLARITY achondroplasia study provided an external untreated control population and reference data.

**Findings:** The population comprised 119 participants. Annualized growth velocity with vosoritide was similar to the average-stature population before puberty. The mean (SD) differences in annualized growth velocity across each integer age (6–16 years) between treated and untreated children were 1.84 (0.38) cm/year in

boys and 1.44 (0.63) cm/year in girls. Three-year comparisons of treated versus untreated children demonstrated an additional height gain of 5.75 cm (95% confidence interval [CI]: 4.93, 6.57) with vosoritide. A significant improvement in upper-to-lower body segment ratio at 3 years of treatment was observed for participants with assessments at age <11 (females) and <12 years (males) versus population-level, age-matched, untreated controls ( $p = 0.0087$ ). The arm span-to-standing height ratio remained consistent with untreated participants. Vosoritide had a favorable safety profile with continuous treatment for up to 6 years (464.05 person-years of exposure). No long-term harms or deaths were observed.

**Conclusions:** Vosoritide treatment was well tolerated and had sustained growth-promoting effects in children with achondroplasia treated for up to 6 years.

**Funding:** This work was funded by BioMarin Pharmaceutical.

## INTRODUCTION

Achondroplasia is the most common form of disproportionate short stature, present in approximately 1 in 25,000 live births.<sup>1,2</sup> It is caused by an autosomal dominant pathogenic variant in *FGFR3* that constitutively activates downstream inhibitory signaling pathways in chondrocytes, leading to impaired endochondral bone growth, functional consequences, and multiple complications.<sup>1,3</sup> The pathogenic *FGFR3* variant occurs *de novo* in approximately 80% of individuals with achondroplasia.<sup>4,5</sup>

The C-type natriuretic peptide down-regulates aberrant *FGFR3* signaling in chondrocytes by inhibiting the MAPK-ERK pathway.<sup>4</sup> Vosoritide is a recombinant analog of the C-type natriuretic peptide that has been engineered to resist degradation and increase the half-life.<sup>5</sup> In murine models of achondroplasia, subcutaneous administration of vosoritide showed increased long-bone and craniofacial growth<sup>5,6</sup> and provided proof of concept that vosoritide might benefit individuals with achondroplasia. Vosoritide is the first and only targeted treatment licensed for use from birth until growth plate closure that addresses the underlying pathway that causes reduced bone growth in individuals with achondroplasia.

An open-label, 104-week, phase 2 trial (study 111-202) and its extension study (study 111-205) in children with achondroplasia showed that vosoritide treatment resulted in sustained increases in annualized growth velocity (AGV).<sup>7</sup> These findings supported a pivotal phase 3, randomized, placebo-controlled trial (study 111-301) that showed a statistically significant improvement in annualized growth velocity after 52 weeks of treatment with vosoritide in children with achondroplasia, with a least squares mean difference in annualized growth velocity between participants in the vosoritide group and placebo group of 1.57 cm/year in favor of vosoritide.<sup>8</sup> This improvement was sustained for 2 years in preliminary analyses of the extension study (study 111-302).<sup>9</sup> Similarly, a randomized, phase 2, double-blind, placebo-controlled trial in children aged <5 years established that vosoritide had a safety profile consistent with that observed in older children and improved the height deficit to a similar extent to that observed in the 111-301 study.<sup>10</sup> Based on this evidence, vosoritide has been approved for use in children with achondroplasia and open epiphyses from birth in the USA, Japan, and Australia and from age  $\geq 4$  months in the European Union and  $\geq 6$  months in Brazil.

A comprehensive understanding of the treatment effect of vosoritide in children with achondroplasia requires evaluation over an extended duration and comparison with outcomes in un-

treated children. Here, we report the long-term safety, tolerability, and efficacy (including effects on linear growth and proportionality) in children with achondroplasia from the phase 3, open-label extension study (study 111-302), treated with daily subcutaneous injections of vosoritide for up to 6 years.

## RESULTS

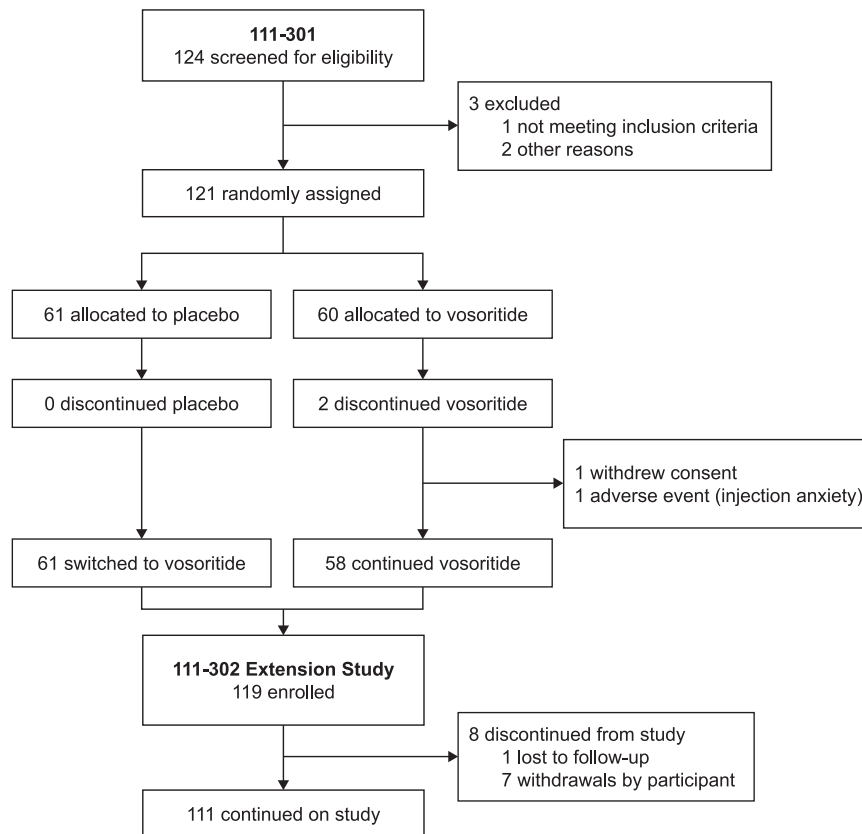
A total of 119 participants entered the extension study and received 15  $\mu\text{g}/\text{kg}$  vosoritide daily (Figure 1; Data S1). By the date of data cutoff (February 25<sup>th</sup>, 2023), 8 participants discontinued from the study: three cited injection burden, two reached near-final adult height, two chose to get limb-lengthening surgery, and one was lost to follow-up. All 61 participants who continued into the open-label extension having been randomized to placebo in 111-301 and who had not discontinued treatment would have had  $\geq 3$  years of follow-up, and 58 of those randomized to vosoritide who continued into the open-label extension and who had not discontinued treatment would have had  $\geq 4$  years of follow-up. The mean (SD) age at day 1 (date of first dose of vosoritide or placebo) was 9.18 (2.60) years (Data S1). The distribution of male to female participants was similar (52.9% versus 47.1%, respectively). Most participants were White (71.4%) and not Hispanic or Latino (93.3%). The mean (SD) upper-to-lower body segment ratio at baseline was 1.98 (0.19), and the annualized growth velocity was 4.01 (1.43) cm/year (Data S1). Most participants (74.8%) were pre-pubertal at baseline (Tanner stage I) (Data S1), and 57/104 (54.8%) participants attained a Tanner stage > I by 3 years (Data S1). The mean height Z scores were 0.28 (0.99), referenced to the untreated-achondroplasia population, and  $-5.12$  (1.09), referenced to the average-stature population (Data S1).

The mean (SD) treatment duration at the time of the data cutoff was 4.0 (0.8) years (minimum: 1.7, maximum: 6.2 years). The mean (SD) adherence while on treatment was 97.3% (4.7%). Of the 119 participants who entered the open-label extension study, 111 (93.3%) remained in the study, and 94 (79.0%) were still on treatment at the time of the data cutoff (Data S1).

### Efficacy outcomes

#### Annualized growth velocity in participants treated with vosoritide was similar to the average-stature population before puberty

Twelve-month interval annualized growth velocity by sex and age in the treated population was similar to the average-stature



**Figure 1. Participant flow**  
Patient disposition in this study.

baseline was assessed (Pearson's  $r$  and  $p$  values) and shown to be  $-0.68$  ( $p < 0.0001$ ) and  $-0.70$  ( $p < 0.0001$ ), respectively (Figures S1 and 3A). Despite this negative correlation, results from the 111-301 study show that irrespective of the baseline annualized growth velocity, there is a clear treatment benefit with greater mean absolute annualized growth velocity at months 6 and 12 in participants treated with vosoritide than in those receiving placebo for each of the baseline annualized growth velocity categories  $\leq 3.5$ ,  $>3.5$  to  $\leq 4.5$ , and  $>4.5$  cm/year (Figure 3B). In the extension study, the mean (SD) absolute annualized growth velocity and change from baseline in annualized growth velocity at year 1 for participants with baseline annualized growth velocity  $\leq 3.5$  cm/year were 5.41 (1.40) and 2.80 (1.55) cm/year, respectively. For participants with baseline annualized growth velocity between  $>3.5$  and  $\leq 4.5$  cm/year, the mean (SD) annualized growth velocity and change from baseline at year 1 were 5.82 (0.92) and 1.80 (0.92) cm/year, respectively. For participants with baseline annualized growth velocity  $>4.5$  cm/year, the mean (SD) annualized growth velocity and change from baseline at year 1 were 5.79 (1.27) and 0.24 (0.21) cm/year, respectively (Table S1).

**A steady increase was observed for height Z scores with a mean improvement of 1 SD for height Z score referenced to untreated achondroplasia at 3.5 years**

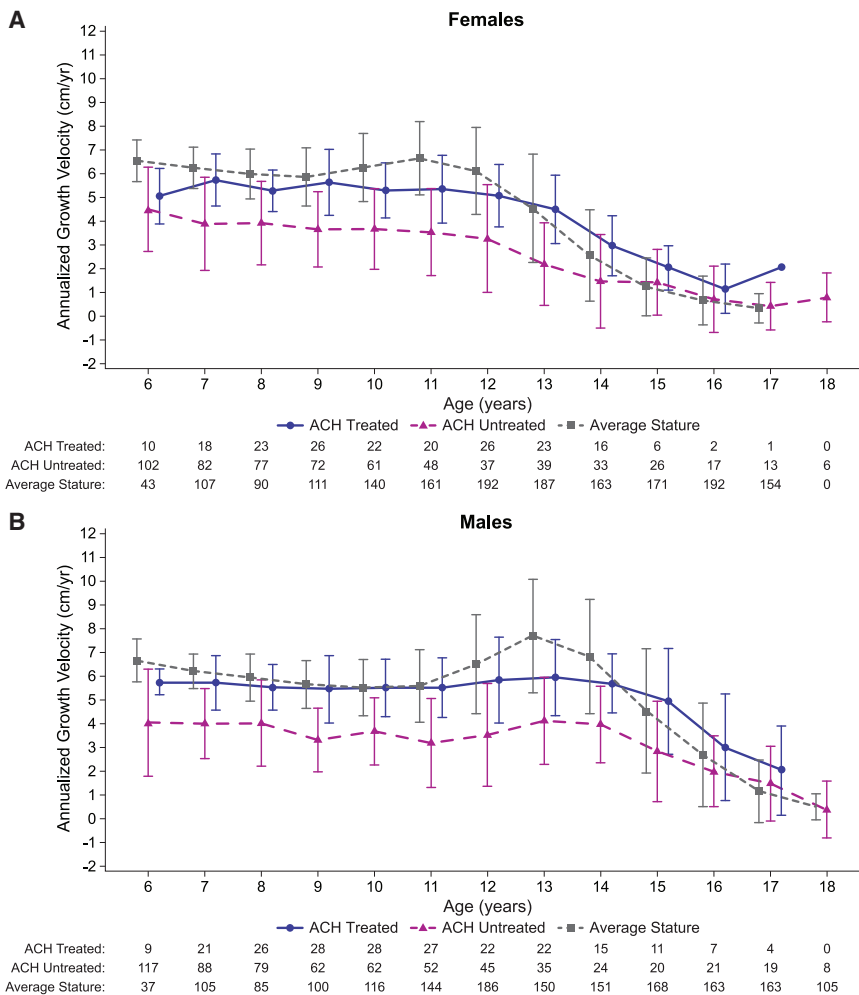
The mean height Z score over time derived using Centers for Disease Control and Prevention (CDC) reference standards for average-stature children<sup>13</sup> and the mean height Z score over time using the achondroplasia reference standard (CLARITY<sup>11</sup>) are shown in Figure S2. A steady increase over time was observed for change from baseline in height Z score when referenced to the untreated-achondroplasia population and the average-stature population (Figure 4). At 3 and 4.5 years, the mean (SD) changes from baseline for the height Z scores referenced to the untreated-achondroplasia population (CLARITY) were 0.89 (0.44) and 1.28 (0.47), respectively. At the same time points, the mean (SD) changes from baseline for height Z scores referenced to the average-stature population (CDC) were 0.59 (0.73) and 0.91 (0.74), respectively (Data S3).

Comparative cross-sectional analyses at 3 years demonstrated a statistically significant height gain for vosoritide-treated participants compared with untreated children with achondroplasia (5.75 cm; 95% confidence interval [CI]: 4.93, 6.57;  $p < 0.0001$ ; Data S3), along with a gain in the

population before puberty and consistently higher than that of the untreated-achondroplasia population (Figure 2; Data S2). The difference between annualized growth velocity for the treated versus untreated populations was compared for each year of age using a two-sample t test with two-sided  $p$  values provided for the test. Up to 15 years of age,  $p$  values were  $<0.05$  (except for females age 5). As growth declines with age, the difference between the treated and untreated groups decreases, and the  $p$  values are no longer  $<0.05$ . Growth in the treated population remained constant during puberty but was lower than that for average-stature children and greater after puberty than in the untreated and average-stature populations. On average, the mean (SD) difference in annualized growth velocities across each integer age (6–16 years) between treated and untreated children with achondroplasia were 1.84 (0.38) cm/year in boys and 1.44 (0.63) cm/year in girls (Data S2). Considering this mean difference in annualized growth velocity, the estimated expected additional height gain for participants treated with vosoritide versus those who are untreated would be 20 cm for boys and 16 cm for girls over the 11-year period from 6 to 16 years of age.

**The greatest change in annual growth velocity from baseline was observed in patients with the lowest baseline annualized growth velocity**

Analyses were performed at 6 and 12 months of follow-up to provide insight into the association between baseline and post-baseline annualized growth velocity. The correlation between baseline annualized growth velocity and change from



**Figure 2. Mean annualized growth velocity by age and sex while on treatment with vosoritide**

(A and B) Mean (SD) annualized growth velocity by age in participants on treatment with vosoritide (111-302 full analysis set), untreated participants with achondroplasia (CLARITY<sup>11</sup>), and average-stature children (Kelly et al.<sup>12</sup>) in (A) females and (B) males. ACH, achondroplasia.

marizing the baseline characteristics of the participants included in each arm, which were shown to be similar (Data S4). The least squares mean difference at 3 years was  $-0.09$  (95% CI:  $-0.15$ ,  $-0.02$ ) in favor of vosoritide with a two-sided descriptive  $p$  value of 0.0087 (Data S4; Figure 6). The least squares mean change for the treated population was  $-0.15$  (95% CI:  $-0.19$ ,  $-0.11$ ), while in the untreated population, it was  $-0.06$  (95% CI:  $-0.11$ ,  $-0.01$ ). The upper limits of the 95% CI for the least squares mean change in both the treated and untreated populations are below zero, indicating that the underlying natural decline in the ratio represents a significant decrease, albeit significantly less than that in the treated arm. Figure 6 provides the observed changes over time in the two comparative arms.

**Arm span-to-standing height ratio consistent with the untreated population**

The arm span-to-standing height ratio remained consistent throughout the study at around 0.89 (Data S5), similar to the ratio for the untreated population (Data S5),<sup>14</sup> showing that arm length increases as overall height increases.

**Safety outcomes**

**15 mg/kg vosoritide daily had a favorable safety profile with continuous treatment up to 6 years (464.05 person years of exposure)**

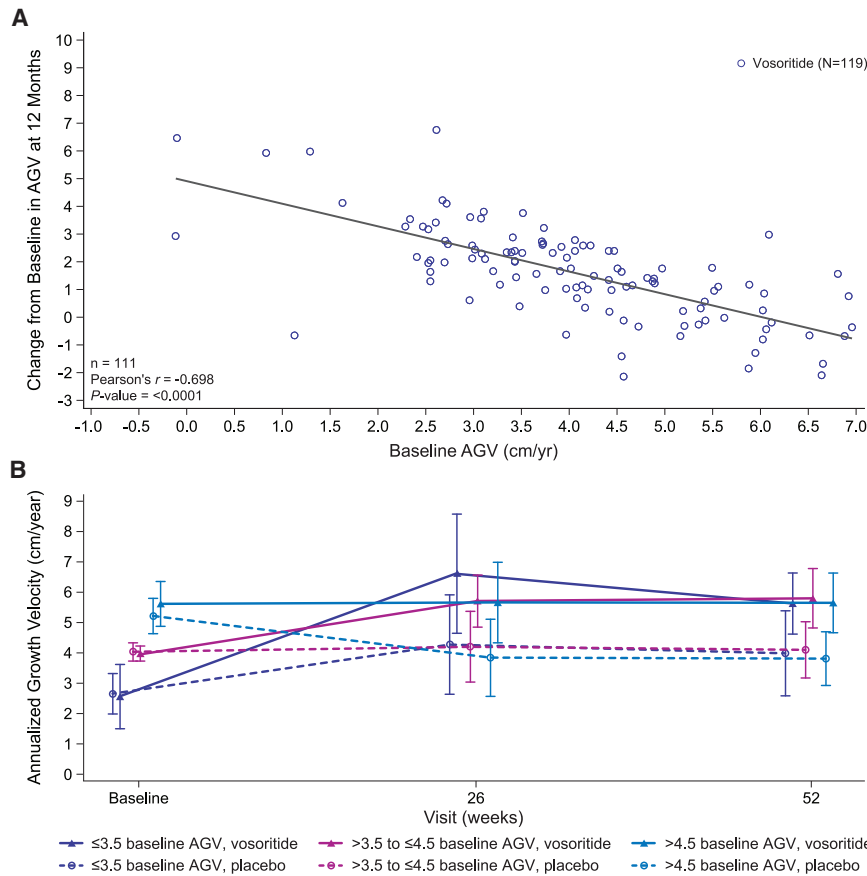
The most common adverse event was nasopharyngitis (0.3 events/person year; Table 1). No long-term sequelae were observed related to daily injections. Serious adverse events occurred in 22 (18.5%) participants and were generally attributed to the underlying condition. No participants died. One participant (0.8%) discontinued vosoritide due to a treatment-related serious adverse event (unresolved cervicothoracic kyphoscoliosis). Treatment-related genu varum occurred in one participant, attributed to growth and underlying joint damage due to achondroplasia. Seven participants (5.9%) experienced a traumatic fracture and continued treatment with vosoritide during healing without complications. Summary tables for the four laboratory bone markers of serum calcium, phosphates, alkaline

average-stature-referenced height Z score (0.82; 95% CI: 0.68, 0.95;  $p < 0.0001$ ; Data S3).

Spaghetti plots by sex of standing height over time for individual participants, plotted against the height reference ranges for the average-stature population and the untreated-achondroplasia population, are shown in Figures 5 and S3.

**Upper-to-lower body segment ratio improved in younger participants treated with vosoritide versus an untreated control arm**

The mean (SD) changes in upper-to-lower body segment ratio at 3 years for each of the three baseline age groups ( $\geq 5$  to  $<8$ ,  $\geq 8$  to  $<11$ , and  $\geq 11$  years) were  $-0.15$  (0.11),  $-0.08$  (0.10), and  $-0.06$  (0.11), respectively (Data S4). At 4.5 years, the mean (SD) changes from baseline were  $-0.18$  (0.16),  $-0.08$  (0.31), and  $-0.03$  (0.12), respectively. Comparative longitudinal analyses were conducted to assess the change in upper-to-lower body segment proportionality for all participants, with a 3-year assessment taken at age  $<11$  years for females and  $<12$  years for males ( $n = 48$ ). The same set of criteria was used to select the participants included in the control from the 111-901 study and the 111-301 placebo arm ( $n = 29$ ). A table is provided sum-



**Figure 3. Association between baseline annualized growth velocity and change from baseline in annualized growth velocity in participants treated with vosoritide**

(A) Change in mean annualized growth velocity at 12 months in participants on treatment with vosoritide (111-302 full analysis set) versus baseline annualized growth velocity.

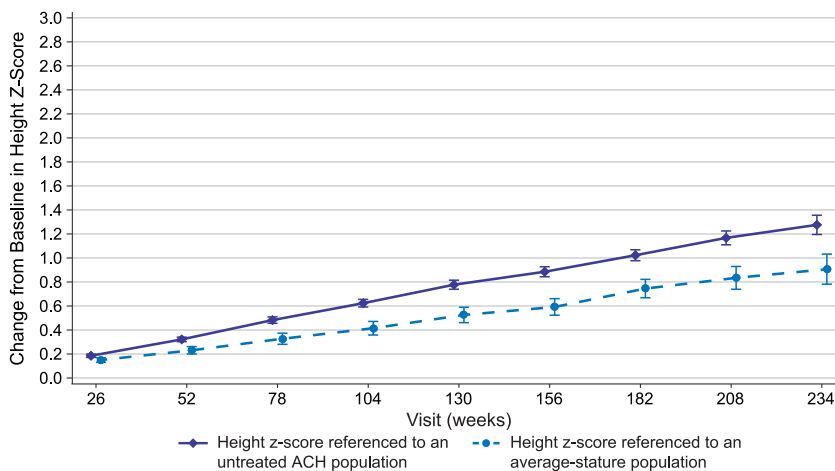
(B) Mean (SD) annualized growth velocity at baseline, 6 months, and 12 months by baseline annualized growth velocity for in patients on treatment with vosoritide versus placebo (111-301 full analysis set). AGV, annualized growth velocity.

phosphatase, and 25-hydroxy vitamin D showed no apparent trends over time (Data S6).

Bone age progressed normally in boys and girls throughout the study (Data S6). The mean (SD) differences in bone age and chronological age at 3 years were  $-0.54$  (1.46) in boys and  $-0.29$  (1.69) in girls and at 4 years were  $-0.61$  (1.55) and  $-0.35$  (1.33),

respectively. The mean (SD) changes from baseline in bone age after 3 years of treatment were 3.20 (1.41) years in boys ( $n = 55$ ) and 3.48 (1.64) years in girls ( $n = 48$ ). Corresponding data at 4 years were 4.32 (1.64) years in boys ( $n = 30$ ) and 4.34 (2.01) years in girls ( $n = 21$ ).

Dual-energy X-ray absorptiometry (DXA) results of whole body less head and lumbar spine bone mineral density (BMD) Z score

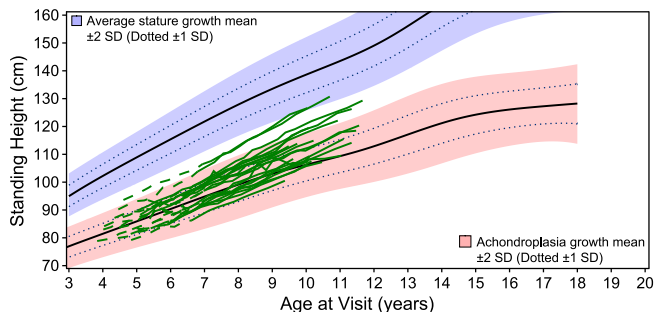


**Figure 4. Change from baseline in height Z score in the treated population referenced to an untreated-achondroplasia population and referenced to an average-stature population (111-302 full analysis set)**

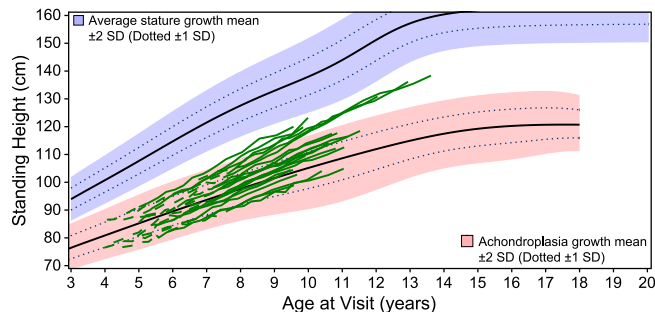
Achondroplasia height Z scores were derived using age-specific reference data (means [SD]) from CLARITY.<sup>11</sup> Average-stature height Z scores were derived using age-/sex-specific reference data (means [SD]) for average-stature children per the Centers for Disease Control and Prevention (CDC).<sup>13</sup>

ACH Treated: 111 111 109 112 109 111 90 53 35

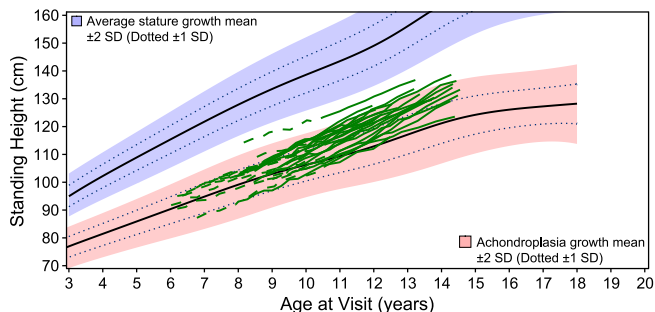
Boys: Years  $\geq 5 - < 8$



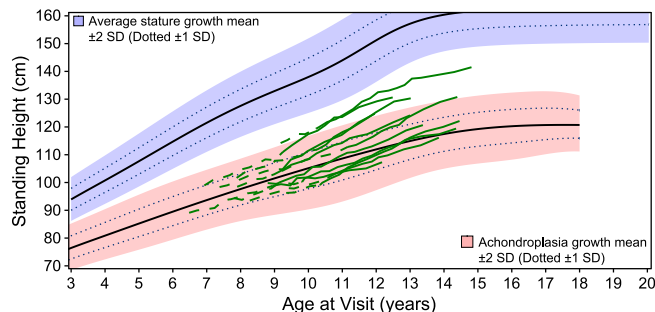
Girls: Years  $\geq 5 - < 8$



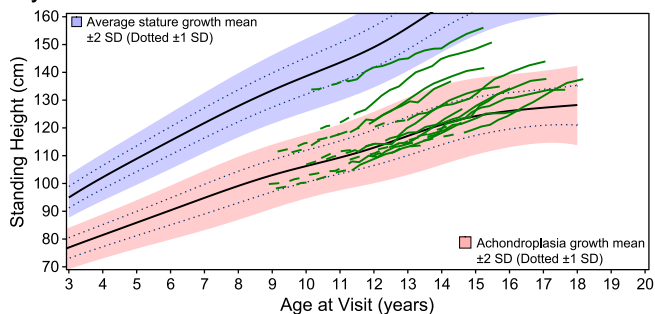
Boys: Years  $\geq 8 - < 11$



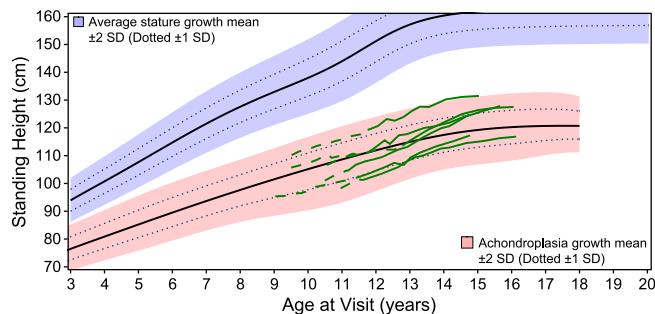
Girls: Years  $\geq 8 - < 11$



Boys: Years  $\geq 11 - < 15$



Girls: Years  $\geq 11 - < 15$



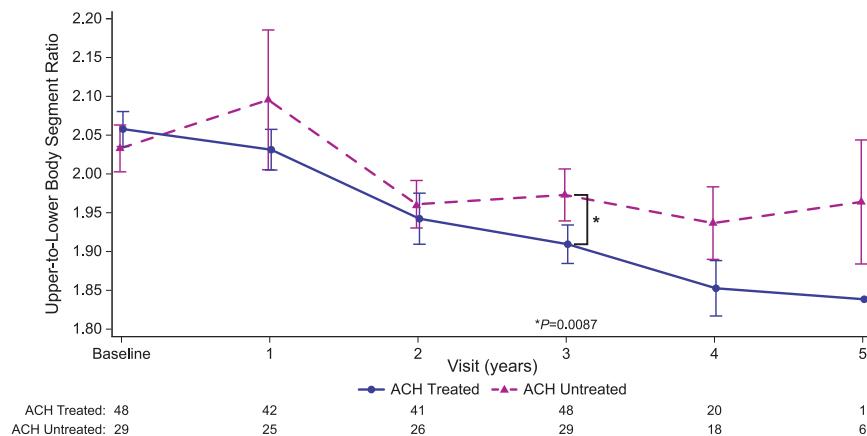
**Figure 5. Spaghetti plot of standing height over time by age group and sex (111-302 full analysis set, in participants continuing on treatment)** “Age at visit (years)” is age at visit of measurement. Dashed lines represent the data before vosoritide treatment, and solid lines refer to the data on vosoritide treatment. Achondroplasia reference is the age-/sex-specific reference data from CLARITY.<sup>11</sup> Average-stature reference is the age-/sex-specific reference data per the Centers for Disease Control and Prevention.<sup>13</sup>

over time are shown in [Data S6](#) and [Figure S4](#). No change in BMD Z scores was observed.

## DISCUSSION

In this long-term, open-label extension study, children aged 5 years and above with achondroplasia treated with daily subcutaneous injections of vosoritide had consistently higher annualized growth velocity compared with untreated children with achondroplasia of the same sex and age, leading to sustained growth over time similar to the average-stature population before puberty. Assessment of cumulative annualized growth velocity demonstrated a strong underlying negative correlation between baseline annualized growth velocity and change from baseline in annualized growth velocity after 6 and 12 months of treatment. This highlights the importance of consideration of

baseline characteristics when evaluating changes from baseline in this population. Yet, despite the difference in the change from baseline across the three baseline annualized growth velocity categories ( $\leq 3.5$ ,  $>3.5$  to  $\leq 4.5$ , and  $>4.5$  cm/year), the absolute annualized growth velocity at year 1 was similar for each of the three baseline categories, comparable to that observed in the average-statured population, and higher than in those who received placebo. It follows that, irrespective of baseline growth velocity, vosoritide increases the annualized growth velocity to a level similar to that of the pre-pubertal average-stature population. Assessment of 12-month internal annualized growth velocity summarized by age and sex showed mean (SD) increases of 1.84 (0.38) cm/year in boys and 1.44 (0.63) cm/year in girls across each integer age, with an estimated additional gain in height of 20 cm for boys and 16 cm for girls over the 11-year period from age 6 to 16 years compared with untreated



**Figure 6. Mean (standard error) upper-to-lower body segment ratio in a subset of children with assessments at age <11 (girls) or <12 years (boys) (younger treated) (study 111-302) and untreated children (study 111-901)**

Assessments beyond these ages are excluded from analysis, given any treatment is expected to have limited impact on proportionality.

the literature for untreated individuals with achondroplasia, which needs to be considered when assessing this endpoint.<sup>17</sup>

The arm span-to-height ratio remained consistent over time at ~0.89 from treatment initiation to the last available observation in this study.

achondroplasia. Annualized growth velocity before puberty approaches the level of the average-stature population but with no obvious growth spurt. An increased mean annualized growth velocity was observed beyond puberty compared with the average-stature and untreated-achondroplasia populations. These findings may help with the assessment of growth potential in children with achondroplasia later in childhood.

An increase from baseline was observed in the height Z score referenced to the untreated-achondroplasia population and average-stature population over time. However, as expected, a continuous stable increase over time was observed in the untreated-achondroplasia-referenced Z score versus the average-stature Z score, which was affected by the different growth pattern of the achondroplasia population, particularly the pubertal growth spurt. Because of this, the untreated-achondroplasia Z score is a more appropriate endpoint for the assessment of long-term sustainability of treatment effect and demonstrated a sustained treatment effect up to 4.5 years, with a mean (SD) change from baseline of 1.28 (0.47).<sup>14</sup>

To assess the gain in height resulting from being treated for 3 years versus receiving no treatment, the comparative analyses versus the untreated population at 3 years demonstrated a gain in height of 5.75 cm (95% CI: 4.93, 6.57). This height gain is aligned with the results from the 1-year comparative analysis in the 111-301 study, where the gain over placebo was 1.57 cm/year.<sup>8</sup>

The average upper-to-lower body segment ratio is 1.7 at birth and decreases to 1.0 at 10 years of age in unaffected children.<sup>15</sup> In achondroplasia, the ratio never reaches 1.0 but still declines from birth up to approximately age 10 years in girls and 11 years in boys; data from Del Pino<sup>16</sup> demonstrate that the ratio is shown to reach 1.94 for girls and 1.84 for boys. In the current study, the greatest change from baseline in the upper-to-lower body segment ratio is observed in younger participants. A comparative analysis at 3 years of treatment duration demonstrated that the participants treated with vosoritide in the younger years (age <11 [female] or age <12 [male]) had greater and statistically significant improvement in body proportionality compared with untreated controls of the same age range, with a least squares mean difference of -0.09 ( $p = 0.0087$ ). This demonstrates an effect greater than the expected natural decline as referenced in

the literature for untreated individuals with achondroplasia, which needs to be considered when assessing this endpoint.<sup>17</sup>

The arm span-to-height ratio remained consistent over time at ~0.89 from treatment initiation to the last available observation in this study. A similar ratio was observed in the 111-901 observational study when assessed by age and sex.<sup>14</sup> These data suggest that the upper limbs grow commensurately with the overall increase in height, which has the potential to improve reach and, consequently, activities of daily living.

Vosoritide was well tolerated with continuous treatment over 464.05 person years of exposure. One participant experienced unresolved cervicothoracic kyphoscoliosis. All fractures experienced during the study were traumatic in nature. The event rate for fractures (0.02 events per person year) was low, and there was no apparent difference in bone age or chronological age in boys or girls.

The data from the present analysis, in which participants aged 5.1 years and up to 15.9 years with achondroplasia received vosoritide daily for a mean of 4 years, are consistent with the findings reported from the phase 2, dose-finding trial<sup>7</sup> and the phase 3, placebo-controlled trial of vosoritide.<sup>8,9</sup> These studies consistently demonstrate that daily vosoritide treatment has a sustained treatment effect. The increase in annualized growth velocity among participants approximated that of average-height children of a similar age and provides further clinical evidence supporting vosoritide as a targeted therapy addressing the underlying molecular pathology in individuals with achondroplasia.

The absence of any observed adverse effects on bone maturation and the significant improvements in upper-to-lower body segment proportionality in the younger population strengthen the prediction that longer periods of treatment commenced at an early age may result in durable effects on skeletal growth and final adult height, with greater improvements in body proportions (as assessed by upper-to-lower segment ratio) and functionality.

In this clinical study, BMD Z scores for whole body less head and lumbar spine often appear, on average, to be low for age and sex (i.e., BMD Z score < -2.0). However, because the BMD Z scores were not adjusted for short stature, they are underestimations of true BMD<sup>18</sup> and should not be interpreted as an increased prevalence of low BMD, or increased risk for later osteoporosis, in achondroplasia. Z scores were not adjusted for short stature, as we evaluated changes in DXA

**Table 1. Incidence of and exposure-adjusted event rates of treatment-emergent adverse events (>10% incidence overall) (111-302 safety population)**

	Overall (N = 119)	
	Incidence n (%) <sup>a</sup>	Event rate n (rate) <sup>b</sup>
Total treatment exposure, person years	–	464.05
Participants with any adverse event	118 (99.2)	1,834 (4.0)
Leading to dose reduction	0 (0)	0 (0)
Leading to drug interruption	41 (34.5)	143 (0.31)
Leading to study drug discontinuation	1 (0.8)	1 (0.00)
Leading to study discontinuation	0 (0)	0 (0)
Leading to study drug or study discontinuation	1 (0.8)	1 (0.00)
Participants with any serious adverse event	22 (18.5)	28 (0.06)
Leading to dose reduction	0 (0)	0 (0)
Leading to drug interruption	11 (9.2)	14 (0.03)
Leading to study drug discontinuation	1 (0.8)	1 (0.00)
Leading to study discontinuation	0 (0)	0 (0)
Leading to study drug or study discontinuation	1 (0.8)	1 (0.00)
Participants with event of special interest		
Injection site reactions CTCAE grade ≥ 2	2 (1.7)	5 (0.01)
Injection site reactions (excluding bruising) lasting >24 h	11 (9.2)	32 (0.07)
Injection site reactions CTCAE grade ≥ 2 or (excluding bruising) lasting >24 h	13 (10.9)	37 (0.08)
Hypotension	16 (13.4)	21 (0.05)
Heart rate change	1 (0.8)	1 (0.00)
Hypersensitivity (SMQ narrow terms)	25 (21.0)	104 (0.22)
Avascular necrosis or osteonecrosis	0 (0)	0 (0)
Slipped capital femoral epiphysis	0 (0)	0 (0)
Fractures	7 (5.9)	8 (0.02)
Preferred term		
Nasopharyngitis	49 (41.2)	126 (0.3)
Pyrexia	46 (38.7)	71 (0.2)
Headache	41 (34.5)	183 (0.4)
Vomiting	33 (27.7)	59 (0.1)
Upper respiratory tract infection	32 (26.9)	47 (0.1)
COVID-19	30 (25.2)	32 (0.1)
Arthralgia	27 (22.7)	51 (0.1)
Pain in extremity	26 (21.8)	48 (0.1)
Cough	24 (20.2)	38 (0.1)
Ear infection	24 (20.2)	51 (0.1)
Ear pain	21 (17.6)	35 (0.1)
Oropharyngeal pain	19 (16.0)	42 (0.1)
Influenza	18 (15.1)	21 (0.0)
Otitis media	18 (15.1)	31 (0.1)
Back pain	17 (14.3)	31 (0.1)

**Table 1. Continued**

	Overall (N = 119)	
	Incidence n (%) <sup>a</sup>	Event rate n (rate) <sup>b</sup>
Vitamin D deficiency	15 (12.6)	19 (0.0)
Abdominal pain upper	14 (11.8)	20 (0.0)
Gastroenteritis	14 (11.8)	15 (0.0)
Viral infection	13 (10.9)	42 (0.1)
Vitamin D decreased	13 (10.9)	14 (0.0)
Asymptomatic COVID-19	12 (10.1)	13 (0.0)
Dizziness	12 (10.1)	18 (0.0)
Nausea	12 (10.1)	18 (0.0)

Adverse events with onset or worsening after the initiation of vosoritide and up to 30 days after the last dose of study drug were included. Only CTCAE grade ≥ 2 injection site reactions and any injection site reaction (excluding bruising) lasting >24 h for injection site reactions with non-missing or partially reported start and end dates are included. CTCAE, Common Terminology Criteria for Adverse Events; SMQ, standardized medical query.

<sup>a</sup>Percentages were calculated using the total number of patients in the safety population as the denominator. Patients with more than one adverse event of the same preferred term were counted only once for that preferred term.

<sup>b</sup>Rate per person year. Exposure-adjusted event rates were calculated by dividing the total number of events by the total treatment exposure. Multiple occurrences of an adverse event with the same preferred term for a patient were counted for each occurrence for that preferred term.

measurements over time rather than define BMD in this analysis.

This study continues to collect information on wider health measures that might be improved by vosoritide treatment in children with achondroplasia, including quality of life, activities of daily living, and frequency and type of medical and surgical interventions, and these data will be compared with registry data of untreated children with the condition, where available. Continued data collection, until participants reach final adult height, will also provide the opportunity to detect any unknown harms associated with long-term vosoritide therapy.

Vosoritide treatment results in sustained growth-promoting effects in children aged 5 years and above with achondroplasia, with evidence of improvement in the upper-to-lower segment ratio beyond the expected natural history. In addition, recently published data have shown that the persistent growth-promoting and body-proportionality-improving effects of vosoritide observed in these children are accompanied by improvements in physical and social aspects of health-related quality of life as assessed by the QoLISSY (Quality of Life in Short Statured Youth) tool after 3 years of treatment, particularly in those children who had the greatest increases in height Z scores.<sup>19</sup> These findings add to the growing dataset of the overall health benefits of vosoritide therapy in children with achondroplasia, underscoring its sustained treatment effect over 6 years of follow-up, demonstrated by an annualized growth velocity that is maintained across all ages and a continuous increase in height Z scores referenced to untreated children with achondroplasia. There were no changes

to the established safety profile over this 6-year follow-up period.

Further studies of vosoritide in achondroplasia are ongoing. A phase 2, open-label extension trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03989947): NCT03989947) is being conducted of vosoritide treatment in infants and younger children with achondroplasia who underwent a 52-week randomized, double-blind, placebo-controlled trial. A randomized, controlled, open-label clinical trial with open-label extension is investigating the safety of vosoritide in infants and in young children with achondroplasia at risk of requiring cervicomedullary decompression surgery ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04554940): NCT04554940). These trials will provide further insights into the long-term treatment effects on body proportionality and growth, as well as how earlier treatment might affect the most severe medical complications, including foramen magnum stenosis with brainstem compression and sudden death.

The limitations of this study are that the longer-term treatment effects of vosoritide on final adult height, functionality, and medical complications require further follow-up to be assessed. Additionally, as all participants in this study commenced treatment at age >5 years, it would be of interest to observe long-term outcomes in children who started treatment <5 years of age. Additional data are needed to ascertain the effect on other non-skeletal complications of achondroplasia. Longer-term outcomes in both populations will be assessed in ongoing open-label extension studies and in the real-world setting. It should be noted that other targeted therapies for children with achondroplasia are under clinical development.<sup>20</sup> Time will tell how these therapies compare to vosoritide in terms of their safety profiles and effects on growth, proportionality, and the medical and surgical complications of this condition.

## RESOURCE AVAILABILITY

### Lead contact

Further information and requests for data should be directed to the lead investigator, Prof. Ravi Savarirayan ([ravi.savarirayan@mcri.edu.au](mailto:ravi.savarirayan@mcri.edu.au)).

### Materials availability

This study did not generate new unique reagents.

### Data and code availability

The data related to the study are reported in the paper and its [supplemental information](#). This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

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## AUTHOR CONTRIBUTIONS

Conceptualization, R.S. and J.R.S.D.; methodology, A.H.-L., S.L., and A.L.; formal analysis, S.L. and A.H.-L.; investigation, R.S., M.I., W.R.W., C.A.B., J.E.H.-F., P.H., L.E.P., K.P., C.E.P., T.K., P.A., Y.K., A.L.-G., M.B.B., J.T.H., and J.M.L.; data curation and unrestricted access to all data, S.L. and

A.H.-L.; writing – original draft, all authors; writing – review & editing, all authors. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility of its content, including the accuracy of the data and the fidelity of the trial to the registered protocol and its statistical analysis.

## DECLARATION OF INTERESTS

All authors were investigators in this clinical trial except for S.L., A.L., I.S., A.H.-L., and J.R.S.D., who are employees of the funder (BioMarin). A.L.-G. has received consulting fees from BioMarin, has participated as a clinical trial investigator for BioMarin and QED Therapeutics, has received speaker fees from BioMarin, MBA, and EAF, and has received travel support from BioMarin and MBA. C.A.B. has received consulting fees from BioMarin and has participated as a clinical trial investigator for Ascendis, BioMarin, and Roche. C.E.P. has received consulting fees from BioMarin, Sanofi, and Takeda, has participated as a clinical trial investigator for BioMarin, Hemoshear, Prevail, and Sanofi, and has received speaker payments from Sanofi. J.E.H.-F. has received consulting fees from Ascendis, BioMarin, Innoskel, QED Therapeutics, and Tyra, has received research grants from Alexion, has participated as a clinical trial investigator for BioMarin, QED Therapeutics, and Pfizer/Therachon, has received speaker fees from Medscape, and has received travel support from BioMarin, QED Therapeutics, and Tyra. J.M.L. has received speaker fees and travel support from BioMarin and has participated as a clinical trial investigator for Ascendis and QED Therapeutics/Bridge Bio. K.P. has received consulting payments from BioMarin, Novo Nordisk, and QED Therapeutics, has participated as a clinical trial investigator for BioMarin, and has received speaker fees and travel support from BioMarin and Novo Nordisk. L.E.P. has received consulting fees from BioMarin, Denali, and Lysogene, has participated as a clinical trial investigator for BioMarin, Pfizer, and Takeda, and has received travel support from BioMarin. M.I. has received consulting fees from Ascendis, BioMarin, QED Therapeutics/Bridge Bio, Sanofi, and Tyra, has participated as a clinical trial investigator for Ascendis, BioMarin, and QED Therapeutics/Bridge Bio, has received speaker fees from Ascendis, BioMarin, Ipsen, QED Therapeutics/Bridge Bio, and Sandoz, and has received travel support from Ascendis, BioMarin, and QED Therapeutics/Bridge Bio. M.B.B. has been an employee and shareholder of Tyra Biosciences, has received consultancy fees from BioMarin, QED Therapeutics/Bridge Bio, and Tyra Biosciences, has received research funding (to his institution) from BioMarin, has participated as a clinical trial investigator for Ascendis, BioMarin, QED Therapeutics/Bridge Bio, and Therachon/Pfizer, and has received speaker fees from Novo Nordisk. P.H. has received consultancy fees from Grace Science, Neurogene, Novel Pharma, Orchard Therapeutics, and Rallybio, has received speaker fees, travel support, and travel grants from BioMarin, has received research funding from Adrenas, Allievex, Amicus, Ascendis, ASPA, Azafaros, BioMarin, Calcilytics, Denali, Grace Science, Homology, Idorsia, JCR Pharmaceuticals, Orphazyme, Prevail, QED Therapeutics, RegenXbio, Sangamo, and Takeda, and has participated as a clinical trial investigator for BioMarin. R.S. has received consulting fees and travel support from Ascendis, BioMarin, and QED Therapeutics and has participated as a clinical trial investigator for Ascendis, BioMarin, QED Therapeutics, and Sanofi. T.K. has received speaker payments from BioMarin and Novo Nordisk and research grants from Eli Lilly. W.R.W. has received consulting fees from BioMarin and has participated as a clinical trial investigator for BioMarin.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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## SUPPLEMENTAL INFORMATION

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## STAR★METHODS

### KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
<b>Chemicals, peptides, and recombinant proteins</b>		
Vosoritide	BioMarin Pharmaceutical	N/A
<b>Other</b>		
111-302 Trial registration	Clinicaltrials.gov (NCT03424018)	<a href="https://clinicaltrials.gov/study/NCT03424018">https://clinicaltrials.gov/study/NCT03424018</a>
111-901 Trial	Savarirayan et al. <sup>14</sup> and <a href="https://clinicaltrials.gov/study/NCT01603095">Clinicaltrials.gov</a> (NCT01603095)	<a href="https://clinicaltrials.gov/study/NCT01603095">https://clinicaltrials.gov/study/NCT01603095</a>
CLARITY study	Hoover-Fong et al. <sup>3</sup>	N/A
REDCap database	Harris et al. <sup>21</sup>	N/A
CDC growth charts	Centers for Disease Control and Prevention, National Center for Health Statistics	<a href="https://www.cdc.gov/growthcharts/clinical_charts.htm">https://www.cdc.gov/growthcharts/clinical_charts.htm</a>

### EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Children participated for  $\geq 6$  months in a baseline observational growth study (study 111–901; [ClinicalTrials.gov](https://clinicaltrials.gov/study/NCT01603095) number, NCT01603095) before being enrolled in a 52-week, double-blind, placebo-controlled, phase 3 study (study 111–301; EudraCT number, 2015-003836-11; [ClinicalTrials.gov](https://clinicaltrials.gov/study/NCT03197766) number, NCT03197766). They were then eligible to enter the open-label extension, during which they received vosoritide at a daily dose of 15  $\mu\text{g}/\text{kg}$  (study 111–302; [ClinicalTrials.gov](https://clinicaltrials.gov/study/NCT03424018) number, NCT03424018). The key eligibility criteria for the 111-301 study were age 5 to <18 years at screening, achondroplasia documented on clinical grounds and confirmed by genetic testing, and enrollment capped with  $\leq 20\%$  in Tanner >I. Participants' information on sex, age, race, and ethnicity was physician-reported. Information on gender and socioeconomic status was not collected.

Of 121 participants enrolled and randomized in study 111–301, 119 were enrolled in the extension study (Figure S5). This manuscript reports data with a cut-off of February 25, 2023, at which time all 61 participants who continued into the open-label extension, having been randomized to placebo in 111–301, could have had at least 3 years of follow-up (barring discontinuation), and all 58 of those randomized to vosoritide who continued into the open-label extension could have had at least 4 years of follow-up (barring discontinuation).

Independent external control data derived from CLARITY, a retrospective natural history study in untreated participants with achondroplasia,<sup>11</sup> were used for comparisons with vosoritide-treated growth and height gain data. In CLARITY, 1374 participants were enrolled at four skeletal-dysplasia centers in the United States. Participants had a molecular or clinical diagnosis of achondroplasia and spanned the pediatric age range with limited data after reaching adult age. Data on >14,000 height assessments were available in the REDCap database.<sup>21</sup> Data were collected to a common protocol using standardized methodologies and an audit trail was documented.

Average stature annualized growth velocity data from age 6 years were provided from Kelly et al.<sup>12</sup> Height Z-scores were referenced to the untreated achondroplasia population (CLARITY) and the average-stature population (Centers for Disease Control and Prevention [CDC]).<sup>13</sup> Data from observational study 111–901<sup>14</sup> and the placebo arm of study 111–301 were used to form an untreated control arm to assess improvement in upper-to-lower body segment ratio and also to interpret changes over time observed in the study in arm-span-to-height ratio.

### METHOD DETAILS

Outcomes described here include cumulative annualized growth velocity categorized by baseline growth levels; height Z-scores referenced to the untreated achondroplasia population (CLARITY) and the average stature population (CDC); upper-to-lower body segment ratio categorized by baseline age levels and arm-span-to-height ratio, both compared with untreated participants with achondroplasia from the 111-901 study. In addition, 12-month interval annualized growth velocity by age and sex are calculated for treated participants, untreated participants with achondroplasia and average stature children.

Safety was evaluated by the incidence of adverse events, grade  $\geq 3$  Common Terminology Criteria for Adverse Events (CTCAE), serious adverse events and events of interest (injection-site reactions, hypotension, hypersensitivity, fractures, heart rate change, avascular necrosis or osteonecrosis, and slipped capital femoral epiphysis) from all 119 participants in the 111–302 safety set and considered all data from the start of vosoritide treatment in study 111–301 or 111–302 up to treatment discontinuation (+30 days) or the data cut off. Mild (CTCAE grade <2) and transient ( $\leq 24$  h) injection-site reactions, and injection site bruising (unless grade  $\geq 2$ ),

were not recorded in the 111-302 study, hence for consistency this reduced reporting was applied programmatically to the data for the participants who started treatment in the 111-301 study. Safety was also evaluated by the assessment of laboratory bone markers, including serum alkaline phosphatase, phosphates, calcium and 25-hydroxy vitamin D levels.

Plain radiographic images of the lumbar spine and lower extremity provided measurements of the spine and long bones of the arms and legs, along with data on growth plates. Dual energy X-ray absorptiometry (DXA) scans reported the bone mineral content, bone mineral density, and associated Z-scores for whole-body-less-head and the lumbar spine. Plain radiographs of the left hand and wrist were used to determine bone age<sup>22</sup> which was compared with the chronological age of each participant over time.

## QUANTIFICATION AND STATISTICAL ANALYSIS

The analyses include on-treatment data for all 119 children in the extension study up to the cut-off date or to 45 days post treatment discontinuation (30 days post treatment for the safety analyses), whichever was earlier. For all analyses, baseline was defined as the last assessment before the first dose of vosoritide; for participants randomized to vosoritide in study 111-301, this was at the start of 111-301, and for those randomized to placebo in study 111-301, this was at the start of study 111-302. Summaries are descriptive with no imputation. The comparative analyses consider follow-up at 3 years because follow-up at this time was complete at the time of data cut-off (February 25, 2023). Whilst the adverse event summaries and the analyses of annualized growth velocity by age and sex consider all on treatment follow-up (i.e., up to 6 years), the summary tables assessing change from baseline include visits up to 4.5 years only due to too few assessments after this time point. Many of these are exploratory analyses from this ongoing study, which will follow participants until they reach final adult height.

Since the change in annualized growth velocity has a strong correlation with baseline annualized growth velocity, cumulative annualized growth velocity is presented by baseline annualized growth velocity, categorized as  $\leq 3.5$ ,  $>3.5$  to  $\leq 4.5$  and  $>4.5$  cm/year. Pearson correlation statistics are provided to quantify the strength of the correlation between baseline annualized growth velocity and change from baseline in annualized growth velocity, which is also presented graphically. A descriptive summary of annualized growth velocity by integer age and sex is also provided. For this analysis, annualized growth velocity was derived for height assessments  $12 \pm 3$  months apart and linked to a specific integer (6–18 years) considering the age at the midpoint of the 12-month interval. In the event a participant had more than one annualized growth velocity associated to a specific integer age, the annualized growth velocity interval with maximum overlap for that summary year was selected. Similarly, data from the CLARITY study<sup>11</sup> provided annualized growth velocity by integer age and sex derived in the same manner for the untreated achondroplasia population. Plots also included mean annualized growth velocity for average-stature children by age and sex, referenced from Kelly et al.<sup>12</sup>

A cross-sectional comparative analysis versus an external control was conducted to determine height and height Z score gain at 3 years. Vosoritide-treated participants were matched uniquely one-to-many by sex and age ( $\pm 1$  month) to participants from the CLARITY study<sup>11</sup> at both baseline and at the 3-year timepoint. In the event the matching algorithm did not result in a unique set of matched untreated individuals for each participant in the vosoritide arm, untreated participants were randomly distributed to be matched to one of the treated participants. The cross-sectional analysis adjusted for baseline differences in height by subtracting the difference at baseline between vosoritide-treated participants and their matched controls from the difference at year 3 between the vosoritide-treated participants and their matched controls. A one sample *t*-test was then applied to determine whether this difference was statistically greater than zero. Note that the cross-sectional approach was chosen rather than longitudinal because natural history studies do not have regular assessments and thus would result in smaller control arms.

Height Z-scores were derived referenced to the average stature population and the achondroplasia untreated population. To derive the average stature referenced height Z score, each measurement of standing height was converted to an age- and sex-appropriate standard deviation (SD) score using the data and macros for average-stature children from the CDC.<sup>13</sup> For the untreated achondroplasia referenced height Z score, each measurement of standing height was converted to an age- and sex-appropriate SD score using a specific reference table provided for deriving height Z-scores available in the CLARITY publication<sup>11</sup>

To assess the effect of vosoritide on the upper-to-lower body segment ratio, this parameter is summarized at each visit, categorized by age at baseline:  $\geq 5$ – $<8$  years,  $\geq 8$ – $<11$  years and  $\geq 11$  years. In addition, change from baseline in upper-to-lower body segment ratio at 3 years was determined in the subset of 111-302 participants with a 3-year assessment at age  $<11$  years (girls) or  $<12$  years (boys). For comparison, a similar subset of untreated participants and assessments were selected from the 111-901 study/111-301 placebo. The control arm could include any participant who was not included in the vosoritide-treated arm for the analysis if they met the age criteria and had 3 years of untreated follow up. An ANCOVA model included the baseline parameters age, sex, height Z score, and upper-to-lower body segment ratio to adjust for baseline differences (note that the baseline of untreated participants corresponded to their earliest assessment at age 5 years or above). Change from baseline in arm-span-to-height ratio was calculated for all 111-302 participants. A summary table was also provided for this parameter from untreated participants in the 111-901 study to provide further insight on the treatment effect.

Of the analyses presented here, changes from baseline in annualized growth velocity, upper-to-lower body segment ratio and arm-span-to-height ratio were predetermined in the statistical analysis plan for the overall population. Post-hoc analyses include the analysis of height Z score derived using achondroplasia age- and sex-specific reference data<sup>11</sup> and the assessment of 12-month interval annualized growth velocity by age and sex. Average stature referenced height Z score is affected by the growth patterns of the reference population,<sup>13</sup> particularly growth spurts at puberty, which is not the case for the height Z score referenced to children with

untreated achondroplasia.<sup>11,14</sup> For this reason, height Z score referenced to the untreated achondroplasia population is expected to give a better understanding of the long-term treatment benefit compared with those referenced to the average stature population, as the changes in achondroplasia-untreated height Z score observed over time would be expected to be due to the treatment received and not the different growth pattern of the reference population.<sup>14</sup> Other post-hoc analyses include summaries of annualized growth velocity by baseline growth categories, which are included to demonstrate the importance of consideration of baseline growth characteristics. Likewise, for the summaries of upper-to-lower body segment ratio, which are summarized by age and the comparative analysis at 3 years.

#### **Ethics declaration**

This study received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC) with reference number HREC/37252. All other institutions represented in this paper received local IRB approval prior to enrollment of the first participant at their institute. Written, informed consent was obtained from all parents/caregivers of enrolled participants as per protocol and IRB requirements.

## ORIGINAL ARTICLE

# C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia

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## ABSTRACT

**BACKGROUND**

Achondroplasia is a genetic disorder that inhibits endochondral ossification, resulting in disproportionate short stature and clinically significant medical complications. Vosoritide is a biologic analogue of C-type natriuretic peptide, a potent stimulator of endochondral ossification.

**METHODS**

In a multinational, phase 2, dose-finding study and extension study, we evaluated the safety and side-effect profile of vosoritide in children (5 to 14 years of age) with achondroplasia. A total of 35 children were enrolled in four sequential cohorts to receive vosoritide at a once-daily subcutaneous dose of 2.5  $\mu\text{g}$  per kilogram of body weight (8 patients in cohort 1), 7.5  $\mu\text{g}$  per kilogram (8 patients in cohort 2), 15.0  $\mu\text{g}$  per kilogram (10 patients in cohort 3), or 30.0  $\mu\text{g}$  per kilogram (9 patients in cohort 4). After 6 months, the dose in cohort 1 was increased to 7.5  $\mu\text{g}$  per kilogram and then to 15.0  $\mu\text{g}$  per kilogram, and in cohort 2, the dose was increased to 15.0  $\mu\text{g}$  per kilogram; the patients in cohorts 3 and 4 continued to receive their initial doses. At the time of data cutoff, the 24-month dose-finding study had been completed, and 30 patients had been enrolled in an ongoing long-term extension study; the median duration of follow-up across both studies was 42 months.

**RESULTS**

During the treatment periods in the dose-finding and extension studies, adverse events occurred in 35 of 35 patients (100%), and serious adverse events occurred in 4 of 35 patients (11%). Therapy was discontinued in 6 patients (in 1 because of an adverse event). During the first 6 months of treatment, a dose-dependent increase in the annualized growth velocity was observed with vosoritide up to a dose of 15.0  $\mu\text{g}$  per kilogram, and a sustained increase in the annualized growth velocity was observed at doses of 15.0 and 30.0  $\mu\text{g}$  per kilogram for up to 42 months.

**CONCLUSIONS**

In children with achondroplasia, once-daily subcutaneous administration of vosoritide was associated with a side-effect profile that appeared generally mild. Treatment resulted in a sustained increase in the annualized growth velocity for up to 42 months. (Funded by BioMarin Pharmaceutical; ClinicalTrials.gov numbers, NCT01603095, NCT02055157, and NCT02724228.)

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**A**CHONDROPLASIA IS THE MOST COMMON form of disproportionate short stature, with a prevalence of 1 in 25,000 live births.<sup>1-5</sup> The condition is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*) that constitutively activates the mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase pathway in chondrocytes, which inhibits endochondral ossification.<sup>6</sup> The hallmark clinical features are short stature with rhizomelic limb-shortening and macrocephaly. Medical complications include hydrocephalus, hypotonia, back and leg pain, conductive hearing loss, and speech delay. Relative tonsillar hypertrophy may result in obstructive sleep apnea and respiratory insufficiency. Foramen magnum stenosis and cervicomedullary compression may result in central apnea, leading to an increased risk of sudden death in infancy.<sup>7-9</sup> Achondroplasia is associated with a condition-specific profile of developmental milestones, functional limitations affecting quality of life, and chronic pain, all of which lead to psychosocial challenges.<sup>8,10-13</sup> Mortality is increased from birth to 4 years of age and in the fourth and fifth decades of life.<sup>14</sup>

No pharmacologic therapies have been approved for achondroplasia, except for growth hormone, which is available for this indication in Japan.<sup>15</sup> Increases in height in children with achondroplasia who are treated with growth hormone occur mainly during the first 2 years of therapy.<sup>16</sup> In a long-term study with a mean follow-up of 10 years, growth hormone therapy in patients with achondroplasia resulted in an increase in final height by a standard deviation of 0.60 (an addition of 3.5 cm) in male patients and by standard deviation of 0.51 (an addition of 2.8 cm) in female patients.<sup>17</sup> The effects of growth hormone on disproportionality are unknown, as are the long-term complications of such therapy.<sup>16-18</sup> Limb-lengthening surgery improves height but does not prevent associated medical complications; in addition, the surgery is controversial because of its invasiveness and high rate of complications.<sup>19</sup>

C-type natriuretic peptide, encoded by *NPPC*, and its receptor, natriuretic peptide receptor 2 (*NPR2*), are potent stimulators of endochondral ossification.<sup>20</sup> Reduced *Nppc* or *Npr2* expression, or lack thereof, in mice results in severe dwarf-

ism due to impaired endochondral ossification.<sup>21,22</sup> Conversely, overexpression of *Nppc* in mice<sup>23</sup> and of *NPPC* in models of human disease<sup>24-26</sup> is characterized by overproduction of endogenous C-type natriuretic peptide<sup>22,27</sup> resulting in sustained skeletal overgrowth. Continuous intravenous infusion of exogenous C-type natriuretic peptide<sup>28</sup> restores the impaired bone growth observed in mice with achondroplasia and increase long-bone growth in wild-type monkeys by inhibiting the *FGFR3*-mediated MAPK signaling pathway,<sup>29</sup> findings that support the potential for C-type natriuretic peptide–based therapy for achondroplasia.

Vosoritide is a recombinant C-type natriuretic peptide analogue that was developed to have a longer half-life than its endogenous form in order to prolong pharmacologic activity.<sup>30</sup> Once-daily subcutaneous administration of vosoritide promotes long-bone growth in juvenile, skeletally normal mice and monkeys and corrects the dwarfism phenotype in mice with achondroplasia.<sup>29</sup> On the basis of promising preclinical findings, the current phase 2 dose-finding study and the still-ongoing extension study were conducted to evaluate the use of vosoritide in children with achondroplasia.

## METHODS

### STUDY DESIGN AND OVERSIGHT

This phase 2, open-label, sequential-cohort, dose-finding study (Study 202, ClinicalTrials.gov number, NCT02055157) was conducted from January 2014 through October 2017 at nine study sites (six in the United States and one each in Australia, France, and the United Kingdom). Eligible children were 5 to 14 years of age at screening, had achondroplasia confirmed by genetic testing, and had completed at least 6 months of a run-in observational growth study (Study 901, NCT01603095) to establish their baseline annualized growth velocity. (Additional details of Study 901 are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Children with fused growth plates were excluded.

Study 202 included a 6-month dose-finding phase followed by an 18-month period during which patients either received an escalated dose or continued to receive their initial dose (Fig. S1

in the Supplementary Appendix). During the initial 6 months, patients were treated in four sequential cohorts with a once-daily subcutaneous dose of 2.5  $\mu\text{g}$  per kilogram of body weight (cohort 1), 7.5  $\mu\text{g}$  per kilogram (cohort 2), 15.0  $\mu\text{g}$  per kilogram (cohort 3), or 30.0  $\mu\text{g}$  per kilogram (cohort 4). On the basis of emerging safety and efficacy data, after 6 months, the dose was increased to 7.5  $\mu\text{g}$  per kilogram and then to 15.0  $\mu\text{g}$  per kilogram in cohort 1 and to 15.0  $\mu\text{g}$  per kilogram in cohort 2; patients in cohort 3 and cohort 4 continued to receive their initial doses (Table S1 in the Supplementary Appendix). The children who completed the 24-month dose-finding study were eligible to enroll in an ongoing long-term extension study in which they continued to receive their preassigned dose of either 15.0  $\mu\text{g}$  per kilogram or 30.0  $\mu\text{g}$  per kilogram (Study 205, NCT02724228). The long-term extension study began before it was registered at ClinicalTrials.gov because of an administrative issue. A total of 2 of 30 patients were enrolled before registration. Data through July 11, 2018, are included in the current report, representing a median duration of follow-up of 42 months (range, 0.3 to 52.0).

Trained caregivers administered vosoritide to patients at their homes. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate. Studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocols were approved by the relevant ethics boards and are available at NEJM.org.

The sponsor, BioMarin Pharmaceutical, designed and funded the studies, analyzed the data, and provided the trial drug. A medical writer paid by the sponsor, whose work was reviewed by the authors, assisted with manuscript preparation. All the authors vouch for the accuracy and completeness of the data, for the adherence of the studies to the protocols, and for the reporting of adverse events.

#### OUTCOMES

The primary objectives were to evaluate the safety and side-effect profile of a once-daily subcutaneous dose of vosoritide and to determine the dose to further investigate in phase 3 studies. Safety was evaluated according to the incidence of ad-

verse events and serious adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), laboratory test results, vital signs, findings from physical examination and clinical hip assessment, electrocardiographic and echocardiographic results, and detection of an antibody response against vosoritide to characterize any effect on safety, exposure, and efficacy (see the Supplementary Appendix). Imaging assessments yielded measurements of the spine and long bones of the arms and legs, along with data regarding growth plate, bone age, and bone mineral density. A data and safety monitoring committee reviewed safety data every 6 months.

Secondary objectives were to evaluate the effects of vosoritide with respect to the change from baseline in annualized growth velocity (centimeters per year), height z scores, and body-segment proportionality. Vosoritide was also evaluated with respect to its pharmacokinetic profile (see the Supplementary Appendix) and biomarkers of drug activity (urinary cyclic guanosine monophosphate [cGMP]) and endochondral ossification (serum collagen X marker [CXM], a degradation fragment of type X collagen).<sup>31</sup> The baseline concentrations of urinary cGMP were established at each trial visit before the vosoritide dose was administered, and the baseline concentration of CXM was established once on day 1 of treatment before the first dose was administered.

#### STATISTICAL ANALYSIS

All the patients were included in the safety and efficacy analyses. The data obtained from the patients while they were receiving treatment were compared with the pretreatment data collected during the observational run-in study.

Data regarding the annualized growth velocity, which were based on measurements of standing height taken every 3 months, were summarized with the use of descriptive statistics, with the annualized growth velocity during the last 6 months of the run-in study serving as the baseline. Standing height was converted to a z score that was appropriate for sex and age according to a comparison with the reference standards of the Centers for Disease Control and Prevention<sup>32</sup>; higher scores reflect improvement. The 95% confidence intervals of the changes from baseline in annualized growth velocity, z scores, and ratio

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.\***

Characteristic	Cohort 1 (2.5 µg/kg) (N=8)	Cohort 2 (7.5 µg/kg) (N=8)	Cohort 3 (15.0 µg/kg) (N=10)	Cohort 4 (30.0 µg/kg) (N=9)	All Cohorts (N=35)
Age at screening — yr					
Mean	7.3±1.6	8.3±2.2	8.0±1.6	6.9±1.2	7.6±1.7
Median	7.0	9.5	8.0	7.0	7.0
Range	5–10	5–10	6–11	5–8	5–11
Age group at screening — no. (%)					
5 to <8 yr	6 (75)	3 (38)	4 (40)	5 (56)	18 (51)
8 to <10 yr	1 (12)	1 (12)	4 (40)	4 (44)	10 (29)
10 to ≤14 yr	1 (12)	4 (50)	2 (20)	0	7 (20)
Sex — no. (%)					
Female	5 (62)	3 (38)	6 (60)	5 (56)	19 (54)
Male	3 (38)	5 (62)	4 (40)	4 (44)	16 (46)
Ethnic group — no. (%)†					
Not Hispanic or Latino	8 (100)	8 (100)	9 (90)	7 (78)	32 (91)
Hispanic or Latino	0	0	1 (10)	1 (11)	2 (6)
Not reported	0	0	0	1 (11)	1 (3)
Race — no. (%)†					
White	7 (88)	6 (75)	5 (50)	6 (67)	24 (69)
Asian	0	1 (12)	3 (30)	3 (33)	7 (20)
Black	1 (12)	0	1 (10)	0	2 (6)
Other	0	1 (12)	1 (10)	0	2 (6)
Tanner stage 1 — no./total no. (%)‡					
Pubic hair development§	7/7 (100)	8/8 (100)	10/10 (100)	9/9 (100)	34/34 (100)
Breast development¶	5/5 (100)	3/3 (100)	6/6 (100)	5/5 (100)	19/19 (100)
Genital development	2/2 (100)	5/5 (100)	4/4 (100)	4/4 (100)	15/15 (100)

\* Plus–minus values are means ±SD. There were no significant between-group differences in the baseline characteristics listed in the table. Percentages may not total to 100 because of rounding. Vosoritide was administered subcutaneously in once-daily doses. Cohort 1 received an initial dose of vosoritide of 2.5 µg per kilogram of body weight; cohort 2, a dose of 7.5 µg per kilogram; cohort 3, a dose of 15.0 µg per kilogram; and cohort 4, a dose of 30.0 µg per kilogram.

† Race and ethnic group were determined by the investigators through specific questioning of parents or guardians of the participating children at enrollment.

‡ Tanner stages range from 1 to 5, with higher stages indicating more advanced pubertal development.

§ Pubic hair development was assessed in all children, except for one boy in cohort 1.

¶ Breast development was assessed in all girls.

|| Genital development was assessed in all boys, except for one in cohort 1.

of the upper-body segment to the lower-body segment were based on one-sample Student's t-tests with the assumption of normality and are considered to be descriptive; no adjustments were made for multiple comparisons.

## RESULTS

### PATIENTS

A total of 35 children (19 girls and 16 boys) with a mean (±SD) age of 7.6±1.7 years (range, 5 to 11)

were enrolled in the four sequential cohorts (Table 1). As of July 11, 2018, the dose-finding study was completed, and 30 patients had been enrolled in the long-term extension study. During the first 6 months of the dose-finding study, 1 patient in cohort 1 withdrew consent, and 1 patient in cohort 2 discontinued treatment because of fear of needles and injections. One patient in cohort 4 was withdrawn after receiving a diagnosis of grade 1, intermittent Wolff–Parkinson–White syndrome, which was identified on routine

electrocardiography; this patient had no associated clinical symptoms and remained asymptomatic with no episodes of supraventricular tachycardia for the duration of participation in the study. During the last 18 months of the dose-finding study, 1 patient in cohort 1 discontinued treatment because of fear of needles and injections, and 1 patient in cohort 2 discontinued treatment because of closure of growth plates. Among the 30 patients who were enrolled in the long-term extension study, 1 withdrew from the study to undergo limb-lengthening surgery.

Forty-two months of efficacy data were available for 6 patients in cohort 1, 6 patients in cohort 2, and 10 patients in cohort 3; 30 months of efficacy data were available for 8 patients in cohort 4. Up to 52 months of safety data were available for 12 patients in cohorts 1 and 2, up to 45 months in cohort 3, and up to 34 months in cohort 4.

#### ADVERSE EVENTS AND SAFETY

During the treatment periods in the dose-finding and extension studies, adverse events occurred in 35 of 35 patients (100%). Common adverse events that occurred during the treatment period are listed in Table 2, and all adverse events are listed in Table S2 in the Supplementary Appendix. All injection-site reactions were mild (grade 1) and transient. Antidrug antibody responses were detected in 14 of 35 patients (40%) at one or more assessment visits. Among the 14 patients in whom an antidrug antibody response had developed, the serum total antibody titers were transient in 7, with the titers declining to undetectable levels, but were sustained in the other 7 patients at the end of the dose-finding study. Neutralizing antibodies were detected in 2 patients at a single visit. No association was observed between antidrug antibody positivity and frequency or severity of hypersensitivity or injection-site reactions.

Blood pressure and pulse rate were monitored frequently after the initial dose was administered. All reductions in blood pressure from test to test were reported as nonserious and transient and resolved without medical intervention; none resulted in interruption or discontinuation of the study-drug regimen. All changes in blood pressure or pulse rate were asymptomatic, except in one patient in cohort 1 who had a single symptomatic hypotensive event on day 281 of the extension study, which was transient and resolved without medical intervention.

During the treatment periods in the dose-finding and extension studies, serious adverse events occurred in 4 of 35 patients (11%) and included grade 3 obstructive sleep apnea, grade 1 tonsillar hypertrophy, grade 3 thyroglossal cyst, and grade 3 syrinx. No deaths occurred. No adverse events related to disproportionate skeletal growth or clinically significant adverse cardiovascular effects were observed. In addition, there were no reports of grade 3 or higher hypersensitivity reactions, and no patients reported adverse events that were consistent with the criteria for anaphylaxis of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network.

#### ANNUALIZED GROWTH VELOCITY

During the first 6 months of treatment, a dose-dependent increase in the annualized growth velocity was observed in the patients who received vosoritide at a dose of up to 15  $\mu\text{g}$  per kilogram (Fig. 1A, and Table S3 in the Supplementary Appendix). At 6 months, increases in annualized growth velocity from baseline were observed in cohort 2 (1.28 cm per year; 95% confidence interval [CI], 0.07 to 2.48), in cohort 3 (2.01 cm per year; 95% CI, 0.58 to 3.44), and in cohort 4 (2.08 cm per year; 95% CI, 0.30 to 3.87) but not in cohort 1 ( $-0.37$  cm per year; 95% CI,  $-1.84$  to 1.10). The changes in annualized growth velocity from baseline in cohorts 3 and 4 were similar, despite a greater-than-dose-proportional increase in plasma exposure to vosoritide (Table S4 in the Supplementary Appendix).

During the extension study, continued administration of vosoritide resulted in a sustained increase in annualized growth velocity for up to 42 months (the time of data cutoff) (Fig. 1B, and Table S5 in the Supplementary Appendix). Bone age progressed normally in all cohorts through 36 months (Table S6 in the Supplementary Appendix).

The annualized growth velocity increased from baseline in all cohorts during each 12-month interval by 1.10 to 2.34 cm per year for up to 42 months (Table S7 in the Supplementary Appendix). Among the patients who received the 15.0- $\mu\text{g}$ -per-kilogram dose, the mean annualized growth velocity was 5.51 cm per year, as calculated between 30 and 42 months. This change represented an annual increase of 1.46 cm (95% CI,  $-0.15$  to 3.07) from baseline. Among the patients who received the 30.0- $\mu\text{g}$ -per-kilogram

**Table 2. Incidence of Common Adverse Events That Occurred during the Treatment Periods in the Dose-Finding and Extension Studies.\***

Adverse Event	Vosoritide Dose Level†				Overall Study Population (N=35)
	2.5 µg/kg (N=8)	7.5 µg/kg (N=15)	15.0 µg/kg (N=22)	30.0 µg/kg (N=9)	
	<i>number of patients with event (percent)</i>				
Injection-site erythema	4 (50)	7 (47)	14 (64)	9 (100)	30 (86)
Injection-site reaction	2 (25)	8 (53)	17 (77)	9 (100)	30 (86)
Pyrexia	4 (50)	2 (13)	13 (59)	3 (33)	19 (54)
Cough	4 (50)	2 (13)	10 (45)	4 (44)	17 (49)
Hypotension	4 (50)	5 (33)	7 (32)	2 (22)	16 (46)
Injection-site swelling	4 (50)	2 (13)	8 (36)	2 (22)	16 (46)
Nasopharyngitis	1 (12)	3 (20)	12 (55)	2 (22)	16 (46)
Headache	4 (50)	3 (20)	8 (36)	3 (33)	14 (40)
Nasal congestion	1 (12)	2 (13)	7 (32)	2 (22)	12 (34)
Upper respiratory tract infection	0	1 (7)	10 (45)	2 (22)	12 (34)
Ear pain	2 (25)	3 (20)	6 (27)	2 (22)	11 (31)
Vomiting	2 (25)	2 (13)	6 (27)	3 (33)	11 (31)
Ear infection	1 (12)	4 (27)	7 (32)	2 (22)	10 (29)
Oropharyngeal pain	1 (12)	2 (13)	7 (32)	1 (11)	10 (29)
Otitis media	1 (12)	0	7 (32)	3 (33)	10 (29)
Pain in arms or legs	1 (12)	0	5 (23)	4 (44)	10 (29)
Injection-site urticaria	1 (12)	2 (13)	3 (14)	4 (44)	9 (26)
Arthropod bite	1 (12)	2 (13)	5 (23)	1 (11)	8 (23)
Fall	2 (25)	1 (7)	4 (18)	2 (22)	8 (23)
Viral infection	0	0	7 (32)	1 (11)	8 (23)
Upper abdominal pain	1 (12)	1 (7)	4 (18)	1 (11)	7 (20)
Rhinorrhea	2 (25)	1 (7)	3 (14)	1 (11)	7 (20)

\* Adverse events with an incidence of at least 20% in the overall study population are shown. Patients who had more than one adverse event within a given preferred term during the treatment period were counted once within that preferred term. Adverse events were coded with the use of preferred terms from the *Medical Dictionary for Regulatory Activities*, version 19.1.

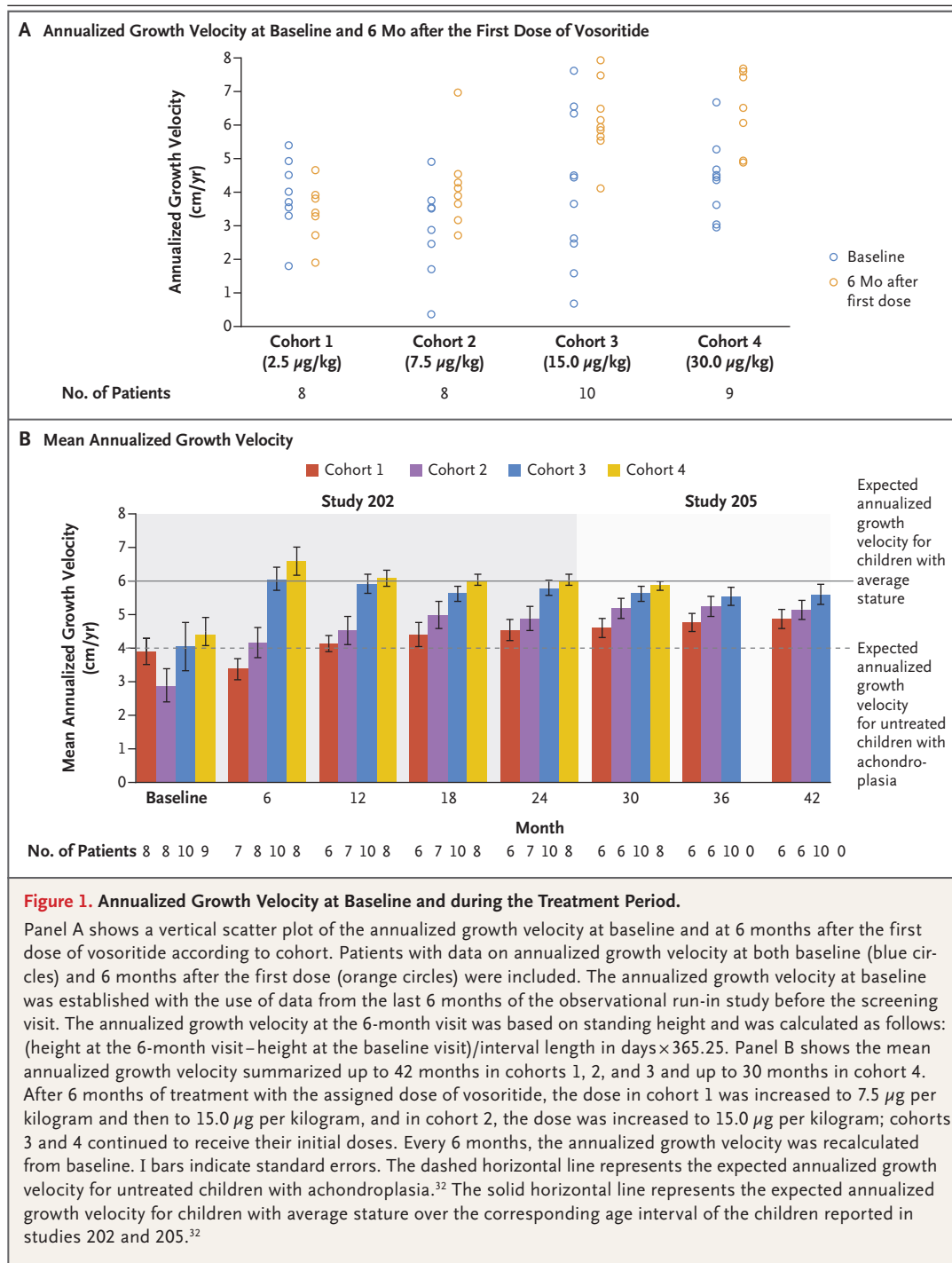
† Patients who received an escalation in dose are summarized in more than one dose column.

dose, the mean annualized growth velocity was 5.60 cm per year, as calculated between 18 and 30 months. This change represented an annual increase of 1.10 cm (95% CI, -0.27 to 2.48) from baseline (Table S7 in the Supplementary Appendix).

#### Z SCORES FOR HEIGHT

Dose-dependent increases in z scores for height were observed in the patients who received a dose

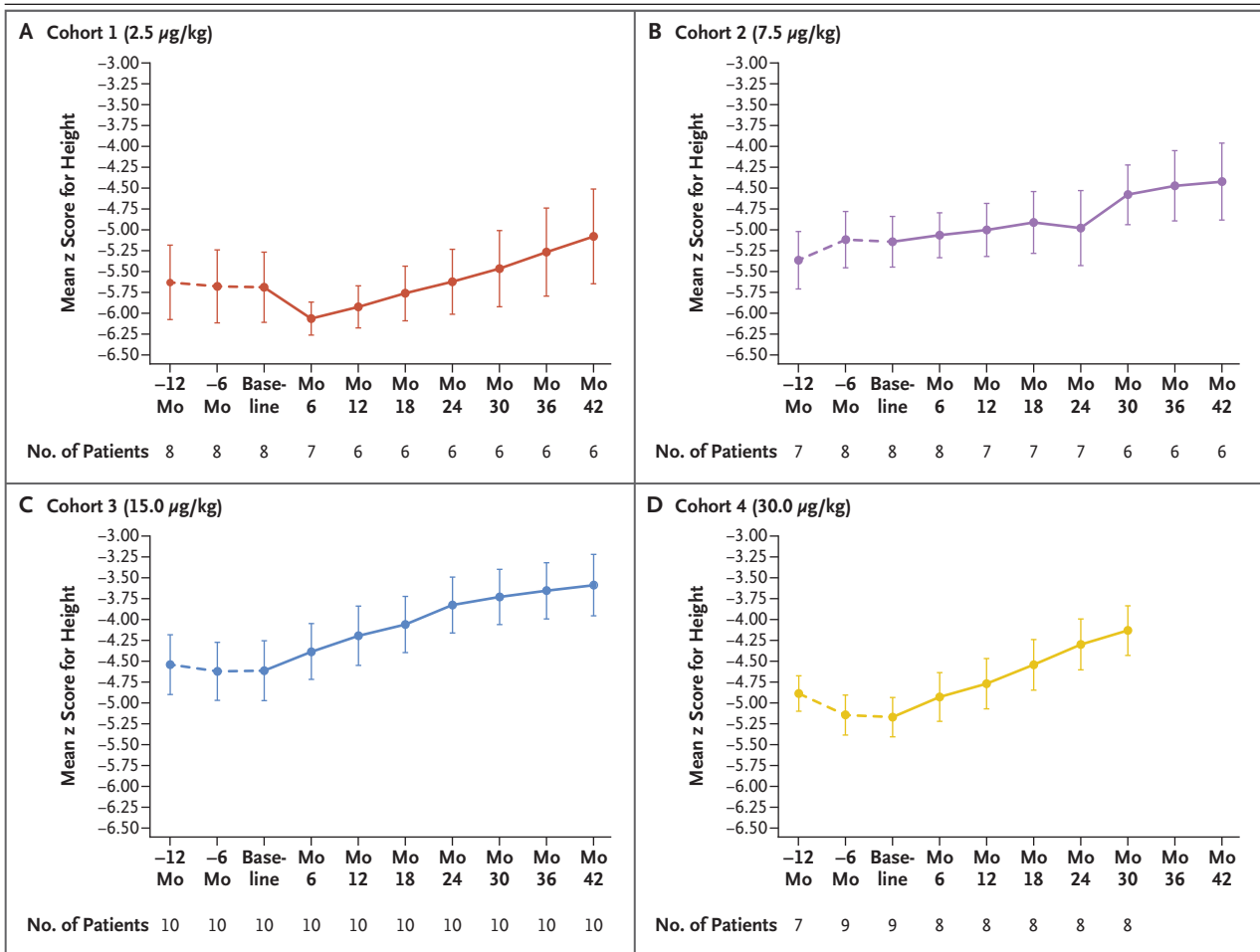
of up to 15.0 µg per kilogram for 6 months; those who received a dose of 30.0 µg per kilogram had an increase similar to that with the 15.0-µg-per-kilogram dose. Vosoritide resulted in a sustained increase in z scores for height for up to 42 months; the mean increase from baseline to 42 months was 0.98±0.99 in cohort 1, 0.49±0.49 in cohort 2, and 1.03±0.57 in cohort 3; the mean increase from baseline to 30 months was 1.06±0.30 in cohort 4 (Table S8 in the Sup-



plementary Appendix). After the baseline observation period had been completed and treatment with vosoritide initiated (Fig. 2), the slopes of the regression lines for the z score were positive (indicating improvement) in all cohorts.

**BODY PROPORTION**

Proportional growth between the upper-body and lower-body segments was observed from baseline to month 42 in cohorts 1, 2, and 3 and from baseline to 30 months in cohort 4. There were



**Figure 2.** Mean z Scores for Height at Baseline and during the Treatment Period.

The figure shows the mean z scores for height during the last 12 months of the observational growth study and during the treatment period in cohorts 1, 2, and 3 through 42 months (Panels A to C) and in cohort 4 through 30 months (Panel D). After 6 months of treatment with the assigned dose of vosoritide, the dose in cohort 1 was increased to 7.5 µg per kilogram and then to 15.0 µg per kilogram, and in cohort 2, the dose was increased to 15.0 µg per kilogram; cohorts 3 and 4 continued to receive their initial doses. The z scores were derived from age- and sex-specific reference data from the Centers for Disease Control and Prevention<sup>32</sup>; higher scores reflect improvement. I bars indicate standard errors. After the baseline observation period had been completed and treatment with vosoritide initiated, the slopes of the regression lines for the z score were positive (indicating improvement) in all cohorts.

no clinically relevant changes in the body-segment ratio (Table S9 in the Supplementary Appendix).

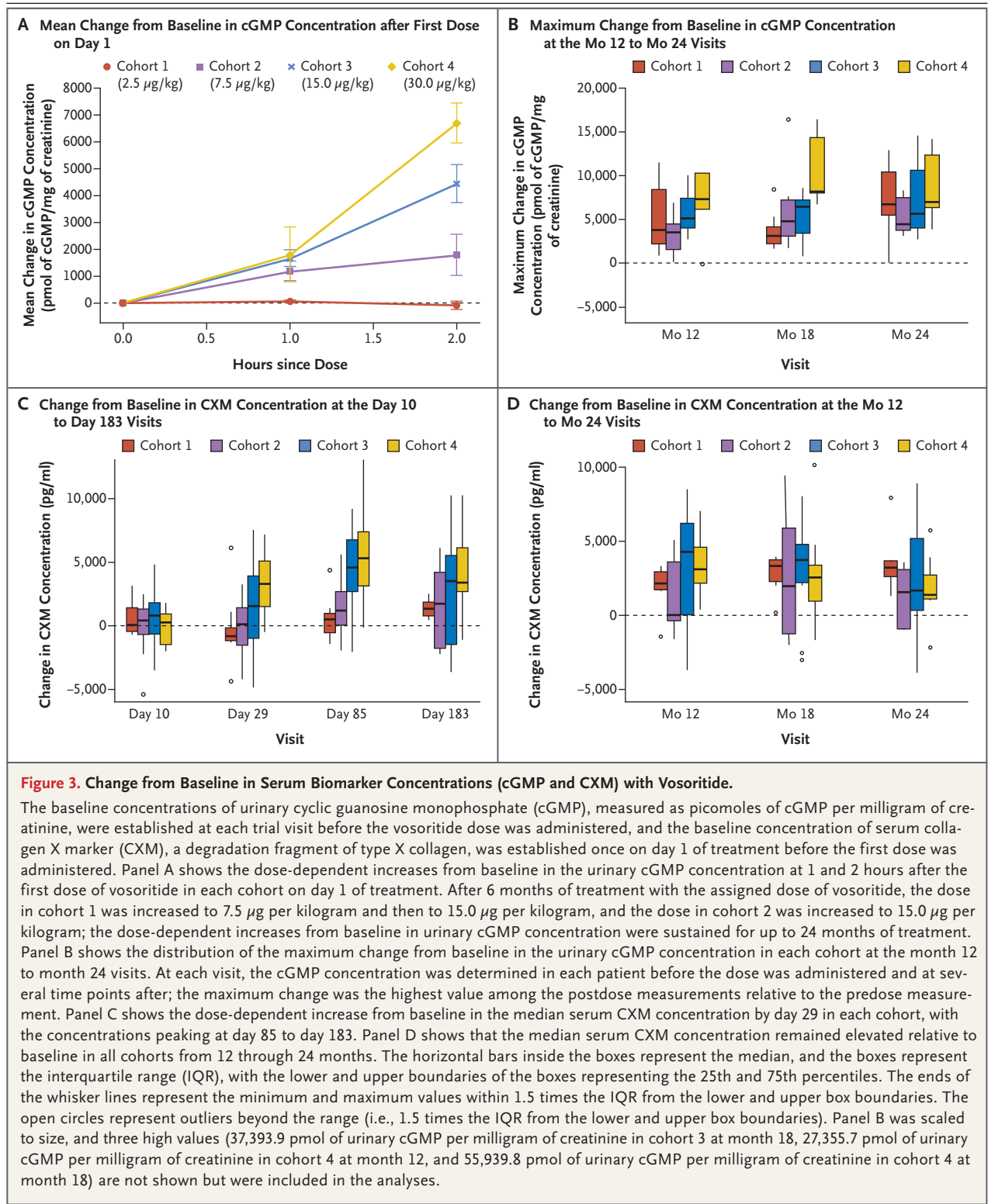
**SENSITIVITY ANALYSES**

Findings from sensitivity analyses of annualized growth velocity and z score for height, in which we used multiple imputation to account for missing assessments of patients who discontinued treatment before 42 months, were consistent with the results of the efficacy analyses reported in the dose-finding and extension studies. Addi-

tional details are provided in Tables S10 through S12 in the Supplementary Appendix.

**BIOMARKERS**

Dose-dependent increases in urinary cGMP and serum CXM concentrations were observed during the initial 6 months of treatment in all four cohorts and remained elevated from baseline through 24 months (Fig. 3). These findings suggests that the pharmacologic activity of vosoritide is sustained over the course of treatment, with the



15.0- $\mu\text{g}$ -per-kilogram and 30.0- $\mu\text{g}$ -per-kilogram doses producing the maximum response.

## DISCUSSION

In this dose-finding study and extension study, vosoritide was administered subcutaneously at once-daily doses ranging from 2.5 to 30.0  $\mu\text{g}$  per kilogram for up to 42 months. Findings from the assessment of the safety and side-effect profile of vosoritide (the primary objective) showed that the most common treatment-related adverse events were mild, transient injection-site reactions. Because C-type natriuretic peptide-based therapy can have vascular effects, pulse rate and blood pressure were monitored, and the results indicated that vosoritide was associated with predominantly mild and transient changes in blood pressure. No bone-related adverse events were observed over the entire treatment period.

Administration of vosoritide resulted in a dose-dependent increase in the annualized growth velocity, up to a dose of 15  $\mu\text{g}$  per kilogram, during the first 6 months (with corresponding dose-dependent increases in biomarker concentrations), and the improvement in annualized growth velocity was maintained over 42 months. By 42 months, improvement in the annualized growth velocity was similar among the patients in cohort 1 (initial dose of 2.5  $\mu\text{g}$  per kilogram, with a dose escalation after 6 months to 7.5  $\mu\text{g}$  per kilogram and then to 15.0  $\mu\text{g}$  per kilogram) and cohort 2 (initial dose of 7.5  $\mu\text{g}$  per kilogram, with a dose escalation after 6 months to 15.0  $\mu\text{g}$  per kilogram). The increased annualized growth velocity observed in the patients who received the 15.0- $\mu\text{g}$ -per-kilogram dose or the 30.0- $\mu\text{g}$ -per-kilogram dose for up to 42 months approximated the annualized growth velocity of average-height children of similar age. Height z scores continued to improve over 42 months, in contrast to the decline observed during the pretreatment period.

Proportional growth between the upper-body and lower-body segments was observed, with no clinically relevant change in the body-segment ratio. An ongoing phase 2, randomized, double-blind, placebo-controlled clinical trial (NCT03583697) of vosoritide in infants and younger children (age range, 0 to <60 months) may provide further insights into the effects of treatment on proportionality and other age-specific achondroplasia-related medical complications.

Available data suggest that C-type natriuretic peptide-based therapy may enhance endochondral ossification and improve skeletal growth in children with achondroplasia. C-type natriuretic peptide-based therapy explicitly addresses the underlying pathophysiologic mechanisms of achondroplasia by down-regulating *FGFR3* signaling through the MAPK pathway and counteracting the effects of constitutively active *FGFR3*.<sup>33</sup> In mouse models, *Nppc* overexpression leads to overgrowth of the axial appendicular and craniofacial skeleton and ameliorates the skeletal, craniofacial, and foramen magnum abnormalities of the achondroplasia phenotype.<sup>23,27,28,30</sup>

A transient dose-dependent increase in urinary cGMP concentration, a biomarker of systemic vosoritide pharmacologic activity, from the predose level to at least 2 hours after the dose was administered was observed on day 1; the transient increase after each dose was sustained throughout the dose-finding study — a finding that indicates durable drug activity. A dose-dependent increase in the median serum CXM concentration, a specific biomarker of endochondral ossification, from the pretreatment level was also observed by day 29; the CXM concentration remained elevated through day 183. In all cohorts, the median serum CXM concentrations were similar and remained elevated from month 12 through month 24. This finding indicates that exposure to vosoritide at the 15- $\mu\text{g}$ -per-kilogram dose results in a sustained and maximum response in serum CXM concentration and is consistent with the near-maximum treatment effect observed with regard to annualized growth velocity at this dose. Together, these findings suggest that the greater systemic pharmacologic activity of vosoritide at the 30.0- $\mu\text{g}$ -per-kilogram dose, as indicated by the urinary cGMP concentration, does not appear to result in additional endochondral ossification, as indicated by the serum CXM concentration.

No difference in efficacy or safety could be identified between the once-daily doses of 15.0 and 30.0  $\mu\text{g}$  per kilogram; thus, our findings support the choice of the lower dose for further evaluation in ongoing studies. A phase 3, randomized, double-blind, placebo-controlled trial (NCT03197766) is currently evaluating the efficacy and safety of the 15.0- $\mu\text{g}$ -per-kilogram dose of vosoritide in up to 110 children (age range, 5 to <18 years) with achondroplasia. An open-label phase 3 extension study (NCT03424018)

will further evaluate the efficacy and safety of vosoritide until patients reach final adult height.

Once-daily subcutaneous administration of vosoritide was associated with a side-effect profile that appeared to be generally mild. Treatment resulted in a sustained increase in the annualized growth velocity for up to 42 months.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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**Pediatric Endocrinology****LBMON196*****A Randomized Controlled Trial Of Vosoritide In Infants And Toddlers With Achondroplasia***

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**Background:** Vosoritide increases annualized growth velocity (AGV) in children with achondroplasia aged 5 to 18 years. This global, phase 2, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of vosoritide on growth in children with achondroplasia aged 3 months to <5 years. **Methods:** This study compared once-daily subcutaneous administration of vosoritide, at doses of 15 or 30 µg/kg of body weight, with placebo. Eligible patients had participated, for up to 6 months, in an observational growth study to calculate their baseline AGV. The primary objective was to evaluate the safety and tolerability of vosoritide in children with achondroplasia. The primary efficacy evaluation was the change from baseline in height Z-score versus placebo at week 52 using an ANCOVA model. Secondary efficacy analyses included change from baseline in AGV and upper-to-lower body segment ratio versus placebo at Week 52 using an ANCOVA model. **Results:** A total of 75 patients were enrolled, with 11 sentinel subjects who received vosoritide to establish

PK and safety. A further 32 were randomized to receive vosoritide and 32 to receive placebo. A total of 73 patients completed the 52-week trial. All patients reported at least one adverse event. Four serious adverse events occurred with vosoritide and 8 with placebo, none were treatment-related. Two participants discontinued, one on vosoritide with pre-existing respiratory morbidity who had a fatal respiratory arrest and one on placebo who withdrew consent. In the full analysis population, vosoritide (n=43) compared to placebo (n=32), increased height Z-score by 0.30 SD (95% CI 0.07, 0.54); increased AGV by 0.92cm/year (95% CI 0.24, 1.59); and did not worsen upper-to-lower body segment ratio which changed by -0.06 (95% CI -0.15, 0.03).

**Conclusions:** Daily, subcutaneous administration of vosoritide to young children with achondroplasia was safe and resulted in increases in height Z-score and AGV. (Funded by BioMarin; ClinicalTrials.gov NCT03583697)

*Presentation:* Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.

# Changes in the Alignment of the Spine and Lower Limb in Children With Achondroplasia Treated With Vosoritide: A Single-center, 1-year Follow-up Prospective Study

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**Background:** Achondroplasia (ACH) is the most common skeletal dysplasia and is characterized by a short-limbed short stature, sagittal spinal malalignment, and genu varum. Vosoritide promotes longitudinal bone growth in children with ACH; however, its effects on various disease-specific complications, other than short stature, are unknown. This study aimed to investigate the therapeutic effects of vosoritide on spinal and lower limb malalignment in children with ACH.

**Methods:** This single-center, open-label, prospective study included patients with ACH aged younger than or equal to 15 years who received vosoritide treatment and had a minimum follow-up period of 1 year. To evaluate alignment after vosoritide treatment, radiologic parameters were measured from sagittal radiographs of the spine and anteroposterior radiographs of the bilateral lower limbs before the administration of vosoritide and 12 months after treatment. Paired *t* tests were used to compare parameters before and after vosoritide treatment.

**Results:** Seventeen patients (mean age,  $7.6 \pm 2.7$  y) were included. After 1-year treatment of vosoritide, the mean height increased by  $5.4 \pm 1.3$  cm. Changes in spinal alignment after 1 year of vosoritide treatment were 1.5 degrees for cervical lordosis,  $-1.3$  degrees for thoracic kyphosis,  $-2.8$  degrees for thoracolumbar kyphosis,  $-5.2$  degrees for lumbar lordosis (LL),  $-2.2$  degrees for pelvic tilt,  $-2.6$  degrees for pelvic incidence,  $-0.4$  degrees for

sacral slope, and 2.6 mm for C7 sagittal vertical axis. Alignment changes in the lower limbs were  $-3.4$  degrees for mechanical axis angle (MAA), 1.7 degrees for mechanical lateral proximal femoral angle (mLPFA),  $-2.8$  degrees for mechanical lateral distal femoral angle (mLDFA),  $-0.2$  degrees for medial proximal tibial angle, and  $-0.5$  degrees for lateral distal tibial angle. The LL, MAA, mLPFA, and mLDFA levels showed statistically significant changes towards the normal range after treatment.

**Conclusions:** One-year treatment of vosoritide decreased the exaggerated LL and improved genu varum deformity in children with ACH. Vosoritide therapy may not only increase longitudinal bone growth but also improve spinal and lower limb malalignment in children with ACH.

**Level of Evidence:** Level II: prospective comparative study.

**Key Words:** achondroplasia, vosoritide, spinal alignment, lower limb alignment

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Achondroplasia (ACH) is caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is a negative regulator of endochondral bone growth.<sup>1,2</sup> Multidisciplinary interventions are required for various disease-specific complications, including upper airway obstructive apnea, foramen magnum stenosis, motor and speech delay, otitis media, and spinal canal stenosis.<sup>3</sup> Musculoskeletal problems during childhood include spinal malalignment and genu varum. The former includes the increase of thoracolumbar kyphosis, exaggerated lumbar lordosis, and “sacrum acutum,” a horizontally tilted body of the sacrum in childhood compared with normal alignment.<sup>4</sup> Persistent spinal malalignment is more likely to cause spinal canal stenosis in adolescence and adulthood.<sup>5</sup> Furthermore, children with ACH show various degrees of severity in genu varum.<sup>6</sup> There is no indication for bracing thereof,<sup>7</sup> and surgical treatments include tibial osteotomy or guided growth technique using tension-band plates.<sup>8,9</sup>

Vosoritide, a human recombinant C-type natriuretic peptide analog, inhibits abnormally activated *FGFR3* signaling and promotes longitudinal bone growth in patients with ACH.<sup>10,11</sup> In 2021, vosoritide was approved for children with ACH by the European Medicines Agency and the US Food and Drug Administration. Several

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K.S. designed the study, collected and analyzed the data, and wrote the manuscript. H.K. designed the study and wrote the manuscript. Y.K. collected the data and revised the manuscript. K.M. reviewed and revised the manuscript. M.M. reviewed and revised the manuscript. S.I. supervised the entire study.

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The authors declare no conflicts of interest.

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clinical trials have demonstrated that vosoritide is well-tolerated and elicits a significant improvement in children's annualized growth velocity.<sup>12</sup> Initially, the treatment was indicated for patients with ACH aged older than or equal to 5 years; the indication has now been expanded to include infants after post-marketing surveillance.<sup>13</sup> However, the effects of vosoritide on various disease-specific complications other than short stature are not known. Therefore, we aimed to conduct a prospective study to investigate the therapeutic effects of vosoritide on spinal and lower limb malalignments in children with ACH.

## METHODS

### Study Design and Patients

This single-center, open-label, prospective study was conducted at our hospital. This study included patients who met all of the following criteria: aged younger than or equal to 15 years, with a documented clinical diagnosis of ACH, received vosoritide treatment, and had a minimum follow-up period of 1 year. Patients who underwent any surgical treatment during the study period, those who had difficulty taking radiographs in the standing position, and those who had no data on annualized growth velocity in the year before the treatment were excluded. This study was approved by the ethical review committee of our institution, and written informed consent for treatment was obtained from all enrolled patients and guardians. Vosoritide treatment was regularly monitored by pediatric endocrinologists and is injected subcutaneously once daily at a dose of 15 µg/kg for patients aged older than or equal to 2 years.<sup>10</sup>

Anteroposterior (AP) and lateral radiographs of the whole spine and an AP radiograph of bilateral lower limbs in the standing position were taken just before administration of vosoritide and at every visit after treatment. To evaluate the alignment of the spine and lower limbs, various radiologic parameters were measured from radiographs before and 12 months after the administration of vosoritide. Standing height and adverse events were investigated at every visit.

### Radiologic Parameters

The following parameters were measured from lateral radiographs of the entire spine: cervical lordosis (CL), thoracic kyphosis (TK), thoracolumbar kyphosis (TLK), lumbar lordosis (LL), pelvic tilt (PT), pelvic incidence (PI), sacral slope (SS), and C7 sagittal vertical axis (SVA) (Fig. 1A).<sup>14–16</sup> For lower limb malalignment, the mechanical axis angle (MAA), mechanical lateral proximal femoral angle (mLPFA), mechanical lateral distal femoral angle (mLDFA), mechanical medial proximal tibial angle (mMPTA), and mechanical lateral distal tibial angles (mLDTA) were measured from AP radiographs of the standing bilateral lower limbs (Fig. 1B).<sup>17–19</sup>

To confirm the reliability of the radiographic measurements in each parameter, intra-rater and inter-rater reproducibility was assessed using an intraclass correlation coefficient (a value > 0.7 was considered acceptable).

## Statistical Analysis

Continuous values are reported with mean and SD [mean ± SD (range)]. Paired *t* tests were used to compare parameters before and after vosoritide treatment. Pairwise Pearson correlation was used to explore the correlations among the parameters. A coefficient value (*R*) > 0.40 was satisfactory [*R* = 0.41 to 0.60 (moderate), *R* = 0.61 to 0.80 (good), and *R* = 0.81 to 1.0 (strong)]. All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY). Statistical significance was set at *P* < 0.05.

## RESULTS

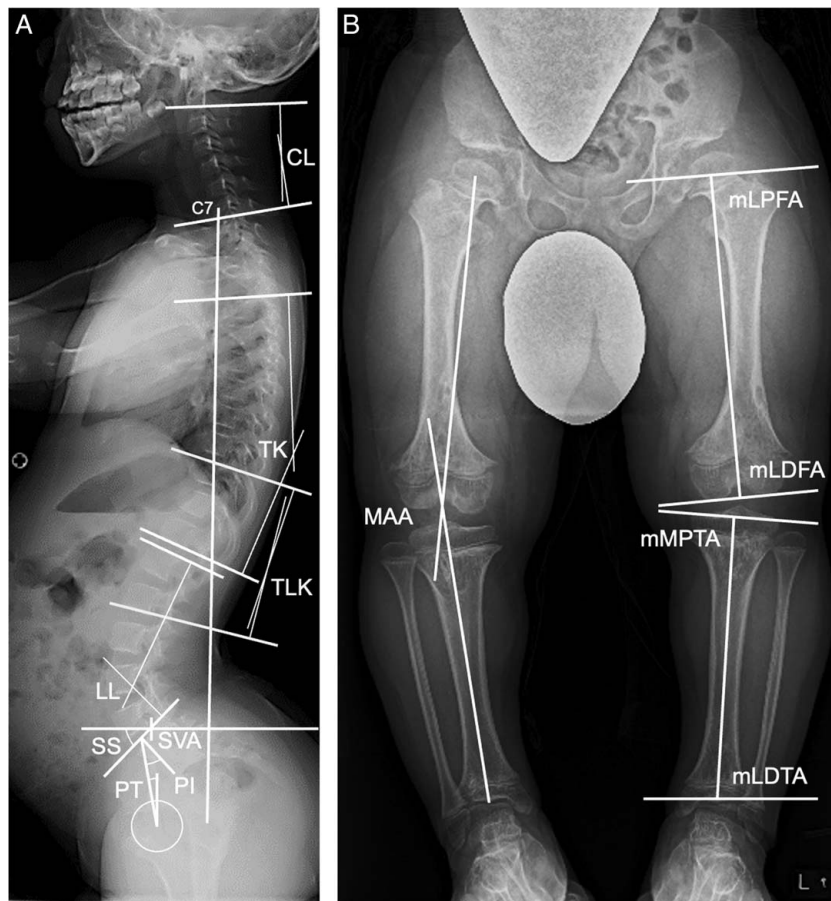
Seventeen patients (8 males and 9 females) met the inclusion criteria. The mean age of patients at the beginning of vosoritide treatment was 7.6 ± 2.7 (3.0 to 12.3) years. Thirteen of the 17 patients had previously received growth hormone therapy (Table 1). After 1 year of treatment with vosoritide, standing height increased by 5.4 ± 1.3 (2.8 to 7.6) cm, and the SD score for height calculated from the growth charts for Japanese achondroplasia children was significantly improved by 0.3 ± 0.2 (−0.2 to 0.8) (Table 2).<sup>20</sup> Minor complications included weight gain in 1 patient and post-injection mood disorder in another, but none of the patients discontinued treatment during the study period.

Values of each radiological parameter in individual patients are shown in Supplementary Table, Supplemental Digital Content 1, <http://links.lww.com/BPO/A878>. Changes in the spinal and lower limb alignment after 1 year of vosoritide treatment are shown in Table 2. In statistical analysis, LL (−5.2 ± 7.0 deg; *P* = 0.01) was significantly decreased (Fig. 2A, B) and MAA (−3.4 ± 4.3 deg; *P* < 0.01) was significantly improved after 1 year of vosoritide treatment, with significant changes in mLPFA (1.7 ± 2.8 deg; *P* < 0.01) and mLDFA (−2.8 ± 3.6 deg; *P* < 0.01) (Fig. 3A, B). All changes in these parameters shifted towards the normal range. There was a moderate and statistically significant correlation between age at treatment and MAA (*R* = 0.56, *P* = 0.02) and mLDFA (*R* = 0.49, *P* = 0.04) (Table 3). This represented a marked improvement in lower limb alignment in younger patients. There was also an appropriate and statistically significant correlation between the increase in height and mMPTA (*R* = 0.63, *P* = 0.01) (Table 3).

Calculation of the intraclass correlation coefficient confirmed the acceptable agreement. Intra- and inter-rater reliabilities were 0.946 and 0.858 for CL, 0.899 and 0.830 for TK, 0.982 and 0.939 for TLK, 0.957 and 0.797 for LL, 0.905 and 0.733 for PT, 0.827 and 0.814 for PI, 0.887 and 0.742 for SS, 0.994 and 0.895 for SVA, 0.984 and 0.898 for MAA, 0.848 and 0.851 for mLPFA, 0.897 and 0.784 for mLDFA, 0.878 and 0.738 for mMPTA, 0.955 and 0.935 for mLDTA, respectively.

## DISCUSSION

The mean improvement in height after 1-year treatment of vosoritide in the current study was 5.4 cm, with an SD score of +0.3. This is consistent with previous



**FIGURE 1.** A standing lateral radiograph of the whole spine (A) and a standing anteroposterior radiograph of bilateral lower limbs (B) were used to determine various radiological parameters. CL, TK, and TLK were measured as the angle between the superior endplate of C2 and the inferior endplate of C7, the angle between the superior endplate of Th2 and the superior endplate of Th12, and the angle between the superior endplate of T10 and the inferior endplate of L2, respectively. LL and SS were measured as the angle between the superior endplate of L1 and the superior endplate of S1 and the angle between the horizontal line along the superior endplate of S1, respectively. The PI was measured as the angle between the line perpendicular to the sacral plate and the line connecting the midpoint of the sacral plate to the midpoint of the femoral head. PT was measured as the angle between the vertical axis arising from the midpoint of the femoral head and the line running from the midpoint of the superior endplate of S1 to the center of the femoral head. C7 SVA was measured as the horizontal distance between a plumb line drawn from the center of C7 and the plumb line from the posterior-superior corner of the sacrum. MAA was measured as the angle between the mechanical axes of the femur (a line joining the center of the femoral head and intercondylar notch) and the tibia (a line joining the midpoint of the tibial eminences and the midpoint of the dome of the talus). The mLPFA was measured as the lateral angle between the mechanical axis of the femur and the line connecting the trochanteric apex and the center of the femoral head. The mLDFFA was measured as the lateral angle between the mechanical axis of the femur and the knee joint line of the femoral condyles. The mMPTA was measured as the medial angle between the mechanical tibial axis and the knee joint line of the tibial plateau. The mLDTA was measured as the lateral angle formed between the mechanical axis of the tibia and the ankle joint line of the distal tibia. CL indicates cervical lordosis; LL, lumbar lordosis; MAA, mechanical axis angle; mLDFFA, mechanical lateral distal femoral angle; mLDTA, mechanical lateral distal tibial angle; mLPFA, mechanical lateral proximal femoral angle; mMPTA, mechanical medial proximal tibial angle; PI, pelvic incidence; PT, pelvic tilt; SS, sacral slope; SVA, C7 sagittal vertical axis; TK, thoracic kyphosis; TLK, thoracolumbar kyphosis.

reports demonstrating that patients treated with vosoritide gained an additional 1.57 cm/year of height, compared with an annual gain of ≈4.0 cm in untreated children with ACH.<sup>11</sup> Increase in the height of ACH children treated with vosoritide may partly be attributed to the improvement of spinal and lower limb alignment, as well as the growth of the long bones themselves. This is the first

report demonstrating that treatment with vosoritide not only increased children’s height in ACH but also changed the standing alignment of the lower limb and spine, particularly with respect to LL and genu varum.

Exaggerated thoracolumbar kyphosis, LL, and sacral inclination are characteristics of patients with ACH. Thoracolumbar kyphosis, which occurs in 94% of infants

**TABLE 1.** Summary of Demographic Data in 17 Patients

Sex (female/male)	9/8
Age at initial treatment (y)	7.6 ± 2.7
Height at initial treatment (SD score)	-4.7 ± 0.9
Previous growth hormone, n (%)	13 (76)
Foramen magnum decompression, n (%)	5 (29)

Age and height are presented as mean ± SD.

with ACH aged younger than 1 year due to a decrease in paraspinal muscle tone, usually resolves spontaneously with skeletal development but persists in ~30% of cases with significant low muscle tone and developmental delay.<sup>21</sup> In contrast, LL and sacral inclination never resolve with growth and progress as a compensatory mechanism for thoracolumbar kyphosis.<sup>5</sup> This concurrent anatomical abnormality could contribute to the development of spinal canal stenosis.

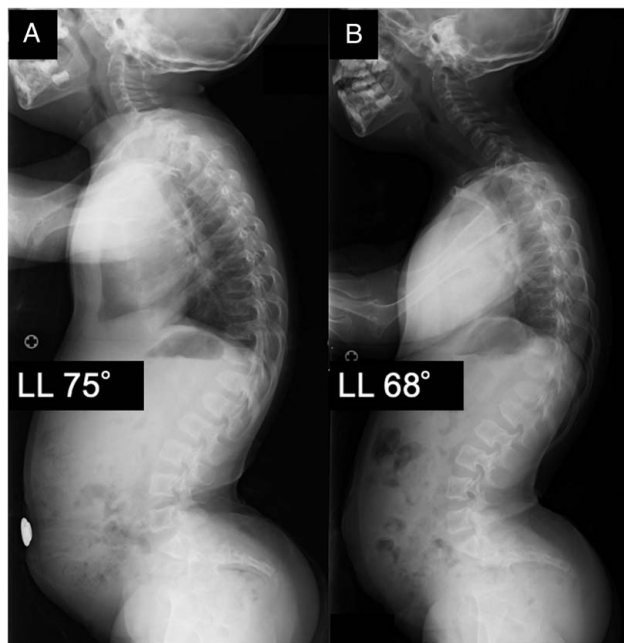
Severe canal stenosis with neurological signs requires spinal decompression surgery, which negatively affects patient quality of life.<sup>22,23</sup> A significant improvement was demonstrated in LL and a slight improvement in TLK after 1-year treatment of vosoritide. There was no apparent effect on the upper spine, possibly because the original upper spinal alignment was within the normal range, even in children with ACH. Alternatively, the difference in growth rates between the upper and lower spine may have caused the lower spine to be more effective. Therefore, the long-term effects of vosoritide on spinal alignment should be investigated.

Genu varum is common in children with ACH, with progression from mild to severe.<sup>24</sup> Incomplete cartilage growth, joint laxity, obesity, and fibular overgrowth have been attributed to this condition.<sup>25</sup> Bracing is not recommended for the treatment of genu varum.<sup>6,7</sup> Surgical treatments include tibial osteotomy, proximal and distal fibular epiphyseal fixation, and guided growth with plates and screws.<sup>9</sup> Vosoritide administration was shown to improve the lower limb deformity, particularly altering the

**TABLE 2.** Comparison of Parameters Between Before and 1 Year After Treatment

	Before	After	Change	P
Height (SD score for achondroplasia)	0.2 ± 1.4	0.5 ± 1.3	0.3 ± 0.2	<b>&lt; 0.01</b>
CL (deg)	11.5 ± 15.8	12.9 ± 9.5	1.5 ± 17.3	0.74
TK (deg)	30.4 ± 15.2	29.1 ± 10.3	-1.3 ± 13.8	0.71
TLK (deg)	27.6 ± 15.8	24.8 ± 15.9	-2.8 ± 7.5	0.15
LL (deg)	53.5 ± 18.5	48.3 ± 19.2	-5.2 ± 7.0	<b>0.01</b>
PT (deg)	6.0 ± 17.8	3.8 ± 18.7	-2.2 ± 8.4	0.30
PI (deg)	56.6 ± 19.9	53.9 ± 19.1	-2.6 ± 9.6	0.31
SS (deg)	50.6 ± 10.9	50.2 ± 9.9	-0.4 ± 4.2	0.69
SVA (mm)	6.6 ± 23.9	9.2 ± 17.0	2.6 ± 17.9	0.26
MAA (deg)	7.3 ± 9.0	3.9 ± 6.8	-3.4 ± 4.3	<b>&lt; 0.01</b>
mLPFA (deg)	83.9 ± 16.8	85.6 ± 16.1	1.7 ± 2.8	<b>&lt; 0.01</b>
mLDFA (deg)	91.6 ± 5.9	88.8 ± 4.1	-2.8 ± 3.6	<b>&lt; 0.01</b>
mMPTA (deg)	88.6 ± 3.4	88.4 ± 2.9	-0.2 ± 1.7	0.49
mLDTA (deg)	95.4 ± 7.0	94.9 ± 6.2	-0.5 ± 2.6	0.27

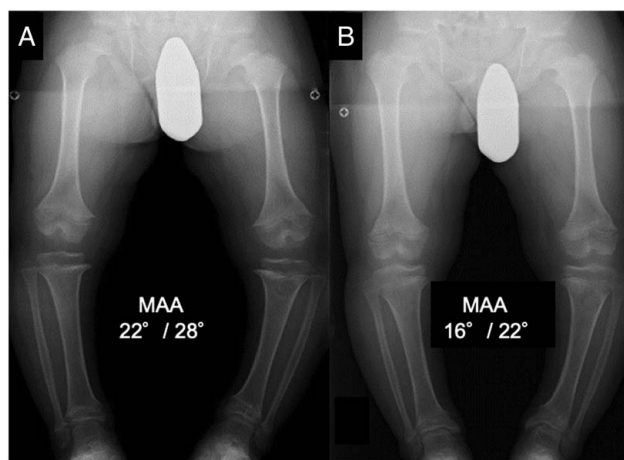
P values with statistically significant differences are in bold. Values are presented as mean ± SD.



**FIGURE 2.** Standing lateral radiographs of the whole spine at 4 years and 5 months before the introduction of vosoritide (A) and after 12 months of treatment with vosoritide (B) demonstrating improvement of lumbar lordosis.

femoral morphology. Moreover, the improvements in MAA and mLDFA levels were remarkable in younger patients. This may be related to the vigorous growth of the femur stimulated by vosoritide in younger patients.

Lower limb malalignment with impaired longitudinal long-bone growth has also been observed in various skeletal dysplasias other than ACH. FGF23-related hypophosphatemic rickets (HPR), which are caused by



**FIGURE 3.** Standing anteroposterior radiographs of bilateral lower limbs at 9 years and 11 months before the introduction of vosoritide (A) and after 12 months of treatment with vosoritide (B) demonstrating improvement of the genu varum deformities.

**TABLE 3.** Correlation of Change Values Between Parameters

	Age	Height	CL	TK	TLK	LL	PT	PI	SS	SVA	MAA	mLPFA	mLDFA	mMPTA
Height	0.01													
CL	0.30	-0.01												
TK	0.18	-0.34	<b>0.56</b>											
TLK	0.17	-0.36	0.33	0.36										
LL	0.33	-0.08	0.04	0.30	0.01									
PT	0.29	-0.19	-0.06	0.20	-0.32	-0.04								
PI	0.15	-0.06	0.08	0.16	-0.39	-0.10	<b>0.80</b>							
SS	-0.24	0.24	0.29	-0.05	-0.25	-0.14	0.06	<b>0.49</b>						
SVA	-0.44	-0.10	0.15	0.23	-0.01	-0.17	0.03	0.10	0.16					
MAA	<b>0.56</b>	-0.21	-0.01	0.25	-0.10	0.26	0.11	0.03	-0.17	-0.29				
mLPFA	-0.11	0.44	0.17	0.04	0.23	0.11	-0.21	-0.22	-0.10	0.24	-0.32			
mLDFA	<b>0.49</b>	-0.36	0.16	0.37	0.01	0.27	0.19	0.17	0.02	-0.29	<b>0.79</b>	<b>-0.54</b>		
mMPTA	0.38	<b>0.63</b>	0.12	-0.10	-0.13	0.15	0.14	0.15	0.07	-0.48	-0.05	0.16	-0.17	
mLDTA	0.28	0.02	0.27	0.18	-0.09	0.42	0.07	0.12	0.14	-0.26	<b>0.50</b>	-0.17	<b>0.63</b>	0.14

Values with statistically significant differences are in bold.

various genetic abnormalities, commonly exhibit short stature and lower limb deformity during childhood.<sup>26</sup> Burosumab, a molecular target drug for FGF23-related HPR, improves not only patient standing height but also lower limb malalignment in children with FGF23-related HPR.<sup>18,27</sup> Further accumulation of data is required, but the use of disease-specific drugs such as vosoritide and burosumab may not only promote longitudinal bone growth but also regulate a physiological growth modulation.

The collection of prospective data without missing data is a strength of this study. Statistically significant differences were found in the MAA and LL despite a short study period. However, long-term follow-up is needed to assess whether these favorable effects are transient or prolonged. This study has several limitations. First, patients aged younger than 3 years were excluded because they seemed unable to undergo radiography in a standing position. Although thoracolumbar kyphosis is an important issue in infants with ACH, we could not investigate the effects of vosoritide on spinal alignment in this age group. Second, the small number of patients and the heterogeneity of the age (3.0 to 12.3 y) are weaknesses of this study. Third, changes in spinal and lower limb alignment were examined after the administration of vosoritide, but the natural progression of alignment in ACH was not compared. Non-randomized study with absence of the control group is another weakness of this study. Furthermore, it was difficult to obtain data on the natural alignment changes because most of our patients had undergone growth hormone treatment. Fourth, although all radiographs were taken using the same protocol, artifacts due to the influence of body position were unavoidable. Finally, the effects of vosoritide on genu valgum deformity, which is occasionally seen in children with ACH, could not be examined because the present study included no children with genu valgum.

In conclusion, 1-year treatment of vosoritide significantly decreased exaggerated lumbar lordosis and improved genu varum deformity in children with ACH. We should continue to follow-up our present cases to

determine the long-term effects of vosoritide on spinal and lower limb alignment.

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### Real-World Safety and Effectiveness of Vosoritide in Children with Achondroplasia: French Early Access Program

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**Research Article**

**Real-World Safety and Effectiveness of Vosoritide in Children with Achondroplasia: French Early Access Program**

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Short Title: Vosoritide French Early Access Program in Children with Achondroplasia

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Keywords: achondroplasia, vosoritide, early access program, growth, safety.

## Abstract

**Introduction:** Vosoritide is the first approved treatment for achondroplasia, a rare genetic disorder that results in disproportionate short stature. In clinical trials, vosoritide has shown a positive safety profile and increased height in children with achondroplasia. This paper shares the organizational structure, initiation, follow-up protocol, and findings of a vosoritide early access program (EAP) conducted in France.

**Methods:** Participants aged  $\geq 5$  years with achondroplasia and open epiphyses were eligible for enrollment in the EAP, conducted by six centers within the French national rare disease reference center for constitutional bone diseases network, from 24 June 2021 to 13 December 2022. Treatment consisted of once daily subcutaneous vosoritide 15  $\mu\text{g}/\text{kg}$ . Safety and effectiveness (height, height Z-score, annualized growth velocity [AGV]) data over a 12-month follow-up period were collected.

**Results:** Among 62 enrolled participants, 57 started treatment with vosoritide within the EAP period with 38 completing at least 6 months and 22 at least 12 months of treatment. After 12 months of treatment, participants achieved a mean AGV of 6.0 cm/year, absolute gain in height of 6.2 cm, and increase in height Z-score referenced to the average stature population of 0.38. All adverse events were mild (mainly injection site reactions) and there were no discontinuations related to vosoritide treatment.

**Conclusions:** In this first use of vosoritide in a real-world setting, vosoritide had a positive benefit-risk ratio similar to that observed in vosoritide clinical trials. The French EAP provides a model that may be adapted and adopted for use in other countries.

Accepted Manuscript

## Introduction

Achondroplasia is a genetic rare autosomal dominant condition with an estimated birth prevalence of 4.6 per 100,000 worldwide and 3.9-6.6 per 100,000 in France [1]. The disease is caused by a pathogenic gain-of-function variant in the fibroblast growth factor receptor 3 (*FGFR3*) gene and at least 80% of cases are spontaneous (*de novo*) [2]; this leads to constitutive activation of the downstream inhibitory signaling pathway in chondrocytes, overwhelming the counteracting signaling from the endogenous natriuretic peptide receptor B (NPR-B) pathway, and resulting in impaired endochondral bone growth [3, 4]. Growth of the long bones is particularly affected resulting in disproportionate short stature, characteristic for achondroplasia [5]. Abnormal linear bone growth significantly contributes to the medical, functional, and psychosocial challenges faced by people with achondroplasia throughout their lifespan [6, 7]. In addition to these growth anomalies, individuals may present with a number of other defects, including bone deformity (e.g., spinal deformity, *genu varum*), ear, nose and throat (ENT) problems (e.g., recurrent ear infections and sleep apnoea), and neurological complications (e.g., foramen magnum stenosis, narrow lumbar canal).

Vosoritide, the first targeted treatment for achondroplasia, is a recombinant C-type natriuretic peptide (CNP) analogue that binds to NPR-B, counteracts *FGFR3* downstream signaling and acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation. Favorable findings from studies of vosoritide in achondroplasia mouse models [8, 9], and a phase 2, open-label, dose-finding study in children with achondroplasia [10] provided support for a phase 3, randomized, double-blind, placebo-controlled, multicenter trial and open-label extension study that evaluated the safety and efficacy of once-daily subcutaneous 15 µg/kg vosoritide in children with achondroplasia aged 5 to <18 years [11, 12]. During the 52-week phase 3 trial, vosoritide was well tolerated with mainly mild adverse events (AEs) and no serious AEs attributable to treatment or on bone maturation [11]; no treatment-limiting AEs emerged after 4 years of continuous treatment in the extension study [13]. After one year of vosoritide treatment, mean annualized growth velocity (AGV) in treated children was 5.61 cm/year, representing a statistically significant increase of 1.57 cm/year compared with placebo ( $p < 0.0001$ ) [11], which was maintained after 4 years [13]. A phase 2, randomized, double-blind, placebo-controlled study of vosoritide in 75 infants and young children (aged 3 months to <5 years) with achondroplasia found that vosoritide was well tolerated and yielded a gain in least-squares mean height Z score from baseline to 52 weeks of 0.25 (95% CI -0.02 to 0.53) relative to placebo [14]. The European Medicines Agency (EMA) designated vosoritide an orphan drug in 2013, issued marketing approval (MA) on 26 August 2021 for its use for the treatment of achondroplasia in patients aged  $\geq 2$  years until closure of epiphyses and expanded the indication to treat children with achondroplasia aged  $\geq 4$  months on 14 September 2023 [15].

France was the first country globally that treated patients with vosoritide outside of a study since approval of an early access program (EAP) by Health Authorities in June 2021 as a pre-marketing authorization EAP (formerly called Cohort Temporary Authorization for Use or cATU) followed by a post-marketing authorization or AP2 in December 2021. In France, EAP prioritized vosoritide treatment to patients aged  $\geq 5$  years and ran until commercialization started on 13 December 2022. This manuscript aims to share the organizational model and follow-up protocol implemented in France for individuals with achondroplasia receiving early access to vosoritide treatment and describe the efficacy and safety of vosoritide in real-world setting.

## Methods

### French EAP Implementation, Common Preparation and Organization at a National Level

The vosoritide EAP was carried out through a consortium of achondroplasia experts within the French national rare disease reference center (CRM) for constitutional bone diseases (MOC) network. The MOC network consists of a coordinating center (Necker-Enfants malades Hospital) and 22 rare disease competence centers (CCMRs) which are intended to provide care and monitoring of patients as close as possible to their homes. The vosoritide EAP was conducted by the coordinating center and five CCMRs in France (University Hospitals of Lyon, Marseille, Nantes, Strasbourg and Toulouse). The consortium was established in January 2021 and met every 3 months to prepare the organization of the EAP, including discussing enrollment criteria, defining baseline and follow-up assessments and visits, and the organization of the EAP; after enrollment began, the consortium continued to meet periodically to share their experiences and follow up.

Medical experts at the six centers reviewed each case of a child with achondroplasia to confirm eligibility for treatment initiation with vosoritide. Children with genetically confirmed achondroplasia aged 5 years or older with open epiphyses were eligible for enrollment in the French EAP from 24 June 2021 to 13 December 2022. Initially, older participants (age  $> 7$  years) were prioritized for enrollment. Prior to the initiation of treatment, each

participant's parent or legal representative/proxy was informed by the prescriber about the medicinal product, the exceptional access procedure, and reporting of adverse effects. Written informed consent was obtained from the participant's parent or legal representative/proxy. Enrollment also required sufficient motivation from the participant and family, commitment to the treatment regimen and follow-up visits, and residing within a reasonable distance from a center providing treatment.

Prior to initiating vosoritide, the treating center checked the results of recent tests (e.g., ENT examination, sleep study, X-rays including bone age, spinal cord magnetic resonance imaging) and conducted teleconsultation visits with the child and parents to assess readiness for treatment, provide caregiver information and training, and ensure that support from healthcare professionals was readily available. Concurrently, participating centers prepared by establishing a well-connected multidisciplinary team, procedures for performing routine follow-up visits, and the logistics and storage arrangements for vosoritide by pharmacies and families.

Treatment of once daily subcutaneous vosoritide at a dose of 15 µg/kg was initiated in a hospital setting (day hospital or specialized consultation) and subsequently self-administered at home by parents/caregivers. Initially during the first month of treatment, the parents were offered home nursing visits to ensure they were educated on subcutaneous injection procedures until they were completely independent.

### **Communication with Participants and Families**

Participants were monitored by the achondroplasia referring medical expert (clinical geneticist or paediatric endocrinologist within the CRMR MOC network) and clinical team at each center. Parents were given a booklet that included instructions for daily parental monitoring of AEs (e.g., documenting symptoms and the associated vosoritide lot number), a list of medical contacts, a certificate of education from the hospital nurse attesting and confirming that the caregiver received the required education, and a letter for the general practitioner and multidisciplinary team informing them that the participant was currently being treated with vosoritide which may require particular vigilance. The follow-up of participants enrolled in the EAP integrated conventional follow-up according to the guidelines of good practice established by the CRMR MOC network over 10 years with more specific follow-up linked to the new treatment.

Motivation and adherence, which are affected by the participant, parent, and caregiver/family context, were assessed and discussed at every visit. Ongoing discussions between the clinical team and participants/parents/caregivers managed expectations by acknowledging that there is individual variability in response to vosoritide; clear stopping criteria based on clinical trial experience (fused epiphysis and AGV < 1.5 cm); uncertainty regarding benefits of treatment beyond an increase in height at that time; evidence of good tolerability and safety but a degree of uncertainty regarding long-term adverse effects. Specific strategies to help motivate participants/families to adhere with treatment and maintain good adherence included: initiating treatment with several children in tandem on the same day at the hospital; conducting therapeutic education workshops for older participants; communicating with family associations; showing measurable benefit on growth parameters; and providing additional support from nurses or other healthcare personnel at participants homes in the early days of home treatment.

### **Data Collection, Monitoring, and Follow-up**

Participants were followed up via clinic visits at months 1, 3 and 6 and at 6-monthly intervals thereafter. Month 1 visit was a virtual visit. Table 1 summarizes the schedule of data collection, monitoring, and follow-up. Baseline characteristics and data on treatment compliance were collected for all enrolled participants. Safety and effectiveness (height, height Z-score, AGV) data over a 12-month follow-up period were collected for participants enrolled during the EAP including assessment of any missed doses. Furthermore, additional height data were collected post hoc at 18-month follow-up. Height Z-scores referenced to the average stature population were derived from data from the Centers for Disease Control and Prevention (CDC) [16], hereafter referred to as CDC height Z-scores. Height Z-scores referenced to the untreated achondroplasia population were derived from a natural history study in that population [17], hereafter referred to as achondroplasia (ACH) height Z-scores. All treated participants were included in safety analyses. During the cATU, all AEs were reported by physicians, inputted into the study database, and coded using the MedDRA system organ class and preferred term. During the AP2, study centers reported de-identified AEs directly to BioMarin as part of routine vosoritide pharmacovigilance. Hence, we summarize the frequency of all AEs reported during the entire EAP (ATUc and AP2) but do not report AEs at the patient level.

Data analyses were descriptive and included the mean, standard deviation (SD), and range for continuous variables and the sample size (N), frequency, and percentage for categorical variables.

## **Results**

## Baseline Characteristics

A total of 62 participants were enrolled with 57 starting treatment within EAP period and 5 starting vosoritide during commercialization (i.e., after 13 December 2022). Of the 57 participants who initiated vosoritide during EAP, 23 (40.4%) began treatment during cATU and 34 (59.6%) during AP2. About half of participants (29/57; 50.9%) were male and the mean (range) age at treatment initiation was 8.6 (5-13) years. Baseline characteristics (Table 2) of the overall sample and subgroup that reached 12 months of treatment during EAP (n=22, 38.6%) were similar except that, as expected, the subgroup with the longest follow-up were slightly older at vosoritide initiation as enrollment of older participants was prioritized early in the EAP (9.6 years [range, 7.7-11.5 years]).

## Treatment Exposure and Adherence

The mean (SD) exposure to treatment was 277 (146) days (range, 32-443 days) for all participants who initiated vosoritide (n=57) during the EAP period. Exposure for the subgroups that completed  $\geq 6$  months (n=38) and  $\geq 12$  months (n=22) of treatment are shown in Table 3.

No patient discontinued treatment. Over 12 months, 14 participants missed a total of 43 doses with 20 missed doses occurring between Month 0 and Month 6 and 23 missed doses between Month 6 and Month 12. One patient was responsible for 16 of the 23 missed doses at Month 12.

## Growth Outcomes

### Participants with $\geq 6$ months of treatment

By the end of EAP, a total of 38 participants (21 males, 17 females) completed at least 6 months of treatment; 36 participants had data on height Z-score and AGV available at Month 6.

The mean (SD) change from baseline to Month 6 in CDC height Z-score and ACH height Z-score, respectively, was 0.20 (0.20) and 0.17 (0.16) in males, 0.27 (0.27) and 0.24 (0.23) in females, and 0.23 (0.23) and 0.20 (0.19) overall. Height increased from baseline to Month 6 by a mean (SD) of 3.0 (0.89) cm in males, 3.4 (1.46) cm in females, and 3.2 (1.19) cm overall. After 6 months of treatment, the mean (SD) AGV was 5.9 (1.65) cm/year in males, 6.5 (2.64) cm/year in females, and 6.2 (2.13) cm/year overall.

### Participants with $\geq 12$ months of treatment

A total of 22 participants (10 males, 12 females) completed at least 12 months of treatment by the end of the EAP. The mean (SD) increase in CDC height Z-score from baseline to Month 12 was 0.38 (0.33) overall with both sexes showing similar improvement (males: 0.33 [0.28], females: 0.42 [0.37]). Figure 1 shows the mean ACH height Z-scores over time by sex. At Month 12, mean (SD) ACH height Z-scores had increased from baseline by 0.30 (0.30) in males, 0.46 (0.21) in females, and 0.39 (0.26) overall. Figure 2 shows absolute height over time by sex. From baseline to month 12, absolute height increased by a mean (SD) of 5.8 (1.71) cm, 6.5 (1.28) cm, and 6.2 (1.50) cm, respectively, in males, females, and overall. After 12 months of treatment, the mean (SD) AGV was 5.7 (1.72) cm/year in males, 6.3 (1.17) cm/year in females, and 6.0 (1.44) cm/year overall.

After the EAP had ended, additional height data at 18 months were available for 17 of 22 participants, collected post hoc during commercial routine treatment. The 17 participants (5 male, 12 female) with 18 months of follow-up height data had a mean (range) age of 9.6 (7.7-11.5) years at initiation of vosoritide. The mean (SD) exposure to treatment was 583 (61) days (range, 390-665 days). From baseline to month 18, height increased by a mean (SD) of 7.5 (1.19) cm, 9.3 (1.33) cm, and 8.8 (1.51) cm, respectively, in males, females, and overall. The mean (SD) increase in CDC height Z-score from baseline to Month 18 was 0.40 (0.30) for males, 0.45 (0.63) for females, and 0.44 (0.55) overall. At Month 18, mean (SD) ACH height Z-scores had increased from baseline by 0.35 (0.28) in males, 0.64 (0.23) in females, and 0.56 (0.27) overall. After 18 months of treatment, the mean (SD) AGV was 5.4 (1.31) cm/year in males, 6.0 (1.00) cm/year in females, and 5.9 (1.10) cm/year overall.

## Safety

Among 57 treated participants, a total of 21 AEs were reported. All AEs were mild and the majority were injection site reactions (Table 4). There were no serious AEs or discontinuations related to vosoritide treatment.

## Discussion

Results from the French EAP, during which vosoritide was administered under real-world conditions to children with achondroplasia aged 5 years or more and open epiphyses, confirm the positive benefit-risk ratio of vosoritide established in clinical trials [10, 11, 18, 12, 19, 14]. A total of 57 participants started vosoritide within the EAP period, at a mean (range) age of 8.6 (5-13) years. After 6 months of vosoritide treatment, 36 participants had anthropometric follow up measurements showing a mean increase of 3.2 cm in height and 0.23 in CDC height Z-score. The 22 participants who reached 12 months of treatment during the EAP period achieved a mean increase of 6.2 cm in height and 0.38 in CDC height Z-score, with a mean AGV of 6.0 cm/year. The descriptive post hoc 18-month outcomes available for 17 participants were in line with earlier findings.

These real-world French EAP outcomes are consistent with the results of a phase 3, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of vosoritide in children with achondroplasia aged 5 to <18 years [11]. In the phase 3 trial, children treated for 12 months with vosoritide obtained a mean (SD) increase from baseline of 0.24 (0.32) in CDC height Z-score versus 0.00 (0.28) for placebo reaching a mean (SD) AGV of 5.61 (1.05) cm/year [11]. The ongoing open-label phase 3 extension study (study 111-302) showed that growth is sustained over 4 years, with no evidence of tachyphylaxis [13]. A phase 2 clinical trial with vosoritide in children aged 3 months to <5 years showed encouraging results: after 12 months of treatment with vosoritide, there was a 0.25 gain in least-squares mean height Z-score change from baseline in the vosoritide group relative to the placebo group (206 study) [14].

Safety findings of mild and transient drug-related AEs (mostly injection site reactions) during the EAP are also consistent with clinical trial data [10, 11, 14], and no new safety signals were observed. As has been reported in vosoritide clinical trials [10-12, 20, 13, 14], participants enrolled in the EAP demonstrated good adherence and none discontinued treatment, improving patients' ability to carry out everyday activities such as self-care. Furthermore, patients and caregivers report consistent improvements from baseline in health-related quality of life, particularly in domains focused on physical function [21]. Additionally, trends toward improvement in foramen magnum area, craniofacial growth, and sinus volume were also demonstrated in infants <6 months of age [14].

American (2005; 2016; 2020) [22-25], Australian (2023) [26], European (2021) [27], Japanese (2020) [28], Spanish (2022) [29], and international (2021; 2022) [30, 31] guidelines for the management of achondroplasia have been published. Early real-world experience with vosoritide, including the French EAP, may help to support practical guidance for the optimal use of vosoritide [32]. A recent paper provided comprehensive considerations for the use of vosoritide in clinical practice based on the early experience of international experts who collectively manage more than 220 patients receiving vosoritide, including suggestions for site preparation, preparation for treatment initiation, support for patients and families, clinical assessments, treatment response, and follow-up [32]. In this paper, the monitoring and follow-up protocol used in the French EAP was cited as an example that could be adopted by other settings with revisions based on patient age and the availability of healthcare resources [32]. We also propose that the CRMR MOC infrastructure used to deliver the French vosoritide EAP offers an organizational model of rare disease management that may be adopted by other countries. Long-term data on the effectiveness and safety of vosoritide are needed to fully understand the risk-benefit profile of this treatment under real-world conditions. Participants who initiated vosoritide during the French EAP are being invited to enroll in a post-authorization safety study (111-603; EUPAS47514; ACORN) to evaluate the long-term safety of vosoritide. ACORN is a European multicenter, non-interventional, retrospective and prospective cohort study that will assess the impact of vosoritide on adverse bone-related safety events, anthropomorphic measures, and achondroplasia-related complications over 10 years [33]. Data from CrescNet ([www.crescnet.org](http://www.crescnet.org)), a German prospective patient registry that has incorporated an achondroplasia diagnosis-specific data set, show that 85 patients treated with vosoritide attained an increase of 0.45 in ACH height Z score during the first year of treatment [34]. As prospective registries will be an important source of long-term data for vosoritide and emerging therapeutic approaches for achondroplasia, capturing data in a standardized manner is essential to allow pooling of datasets from different centers, regions, and countries [35].

### Conclusion

Outcomes reported in this first worldwide use of vosoritide in real-world settings indicate that vosoritide has a positive benefit-risk profile consistent with clinical trial data. The French rare disease management organizational structure and EAP initiation and follow-up protocol provide models that may be adapted and adopted for use in other countries. The specificity of the French network of MOC centers ensured the organization and implementation of a common process on early access to vosoritide treatment to avoid loss of opportunity for children with achondroplasia in France, in an equitable manner at national level, optimizing compliance and follow-up. Real-world studies designed to evaluate the long-term effectiveness and safety of vosoritide are underway and will enable a more complete picture of vosoritide impact on patients with achondroplasia.

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## Statement of Ethics

The Early Access program was approved by HAS France\* and carried out under the conditions authorised by the European General Data Protection Regulation (GDPR) and the amended law of 6 January 1978 known as the 'Informatique et Libertés' law, in compliance with CNIL French formalities on the French Public Health Code concerning early access to medicines.\*\*

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\*\*[Référentiel « accès précoce » | CNIL](#)

Prior to the initiation of treatment, each participant's parent or legal representative/proxy was informed by the prescriber about the medicinal product, the exceptional access procedure, and reporting of adverse effects. Written informed consent was obtained from the participant's parent or legal representative/proxy.

## Conflict of Interest

VCD: consultant/speaker honoraria from IPSEN Pharma, BioMarin, and Mereo BioPharma

TE and BI: consultant/speaker honoraria from BioMarin

MR: consultant/speaker honoraria from BioMarin

ES: hospitality from Abbott Medical France SAS, speaker honoraria and hospitality from Sanofi Aventis France, speaker honoraria from BioMarin

SS: consultant/speaker honoraria and hospitality from Sanofi Aventis France and BioMarin

GB: consultant/speaker honoraria from IPSEN Pharma, Inozyme Pharma Inc. and Exafield, consultant/speaker honoraria from BioMarin

SM and JMP are full-time employees of BioMarin and own stocks in the company.

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## Author Contributions

VCD, TE, BI, MR, ES, SS, and GB were investigators in the EAP. SM and JMP are employees of the funder (BioMarin Pharmaceutical Inc.). VCD, TE, BI, SM, JMP, MR, ES, SS, and GB participated in the interpretation of data and article development.

## Data Sharing

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available upon request to the corresponding author. Investigators will be able to request access to these data and supporting documents via [www.BioMarin.com](http://www.BioMarin.com) beginning 6 months and ending 2 years after publication. An official report of EAP is already publicly available at the HAS site : [https://www.has-sante.fr/jcms/p\\_3385532/en/voxzogo-0-4-0-56-1-2-mg-vosoritide-achondroplasia#ancreDocAss](https://www.has-sante.fr/jcms/p_3385532/en/voxzogo-0-4-0-56-1-2-mg-vosoritide-achondroplasia#ancreDocAss)

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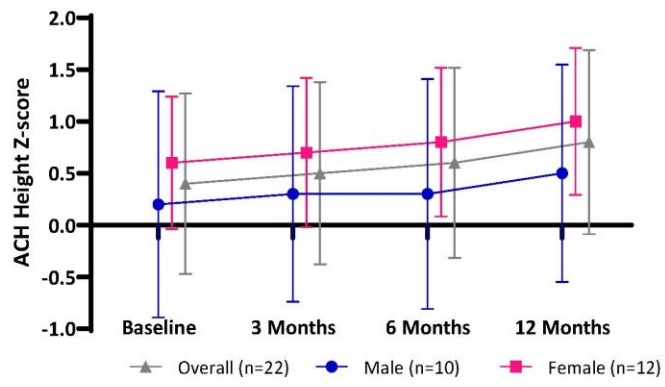
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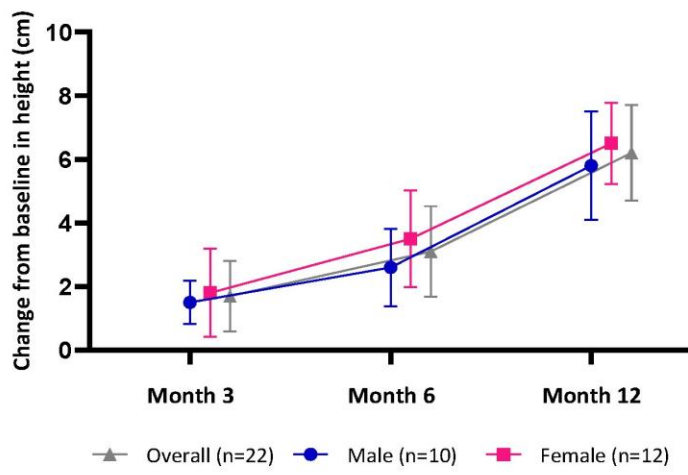
### Figure Legends

Fig. 1. Height Z-scores change from baseline for participants treated for 12 months referenced to untreated achondroplasia (ACH) population. Error bars represent standard deviation.

Fig. 2. Change in baseline in height for participants treated for 12 months. Error bars represent standard deviation.

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**Table 1. Data collection schedule**

	Treatment access request	Day 0 visit (start of treatment)	Month 1	Month 3	Month 6, then every 6 months	End of follow-up
Documentation of achondroplasia <sup>a</sup>	X					
Demographics	X		X		X	
Physical examination	X			X (annual examination)		
Anthropometric and morphological measurements		X		X (annual examination)		
X-ray of the left hand and/or knee <sup>b</sup>	X			X (annual examination)		
Tanner Stage		X <sup>c</sup>		X	X	X
Vosoritide treatment <sup>d</sup>		X	X	X	X	X
Adverse event data <sup>e</sup>			X	X	X	X
<p><sup>a</sup> Documentation included the participant's age at diagnosis, the place, date and author of the diagnosis, and confirmation of genetic testing.</p> <p><sup>b</sup> From 7 years of age. Only if this examination was performed as part of recommended treatment.</p> <p><sup>c</sup> Prepubertal stage without closure of the epiphyseal cartilage in participants aged 7 to 12 years.</p> <p><sup>d</sup> Including dose monitoring.</p> <p><sup>e</sup> All safety events were reported to vosoritide sponsor within 24 hours of identification.</p>						

**Table 2. Baseline demographics and characteristics**

	<b>Overall Treated (n=57)</b>	<b>Treated for 12 months (n=22)</b>
Sex, n (%)		
Male	29 (50.9)	10 (45.5)
Female	28 (49.1)	12 (54.5)
Age at first dose (years)		
Mean (SD)	8.6 (2.0)	9.5 (1.9)
Range	5-13	7-13
Height Z-score, mean (SD)		
Male	-5.2 (1.11)	-5.1 (1.11)
Female	-5.0 (0.96)	-4.9 (0.75)
Overall	-5.1 (1.04)	-5.0 (0.91)
Tanner Stage, n (%)		
I	31 (54.4)	13 (59.1)
II	2 (3.5)	0 (0.0)
Missing	24 (42.1)	9 (40.9)

SD, standard deviation.

**Table 3. Vosoritide exposure**

<b>Exposure to vosoritide (days)</b>	<b>Overall (n=57)</b>	<b>≥6 months (n=38)</b>	<b>≥12 months (n=22)</b>
Cumulative exposure	15,817	15,203	9802
Mean (SD)	277.5 (146.24)	400.1 (81.20)	445.5 (15.90)
Min, Max	32, 443	226, 463	421, 463

SD, standard deviation.

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**Table 4. Number of Adverse Events**

<b>System Organ Class/Preferred Term</b>	<b>Number of events</b>
All adverse events	21
Injection site reaction	14
Injection site erythema	4
Injection site papule	3
Injection site rash	4
Injection site pain	2
Injection site swelling	1
Gastrointestinal disorders	3
Vomiting	3
Skin and subcutaneous tissue disorders	2
Contact dermatitis	1
Erythema	1
Nervous system disorders	2
Headache	1
Presyncope	1



# Real-World Safety and Effectiveness of Vosoritide in Achondroplasia: Results from a Single Center in Portugal

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## ABSTRACT

**Introduction:** Achondroplasia, the most common skeletal dysplasia, is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Vosoritide, a C-type natriuretic peptide analog, is a first-in-class targeted treatment for achondroplasia that counteracts overactive *FGFR3* signaling to stimulate endochondral bone growth. This retrospective cohort study evaluated growth, safety, and treatment

**Prior Presentation:** This manuscript is based on data that have previously been presented at the 16th International Skeletal Dysplasia Society (ISDS) Annual Meeting (September 18–21, 2024) in Madrid, Spain.

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compliance in children with achondroplasia receiving vosoritide under an early access program in Portugal.

**Methods:** Twenty-seven children aged 2–14 years with a genetically confirmed diagnosis of achondroplasia were treated with vosoritide at a single Portuguese center for at least 6 months between January 2022 and June 2024. The analysis included children with severe achondroplasia-associated complications. Anthropometric measurements collected to characterize the effect of vosoritide on growth included height standard deviation score (SDS) and annualized growth velocity (AGV). Student's *t* test was used for statistical comparisons. Safety and tolerability endpoints included adverse drug reactions and treatment adherence.

**Results:** In total, 15 children completed at least 24 months of treatment. After 24 months of treatment, mean variation in height SDS increased from baseline by +0.95 SD ( $P \leq 0.0001$ ), referenced to an untreated achondroplasia-specific population, and +0.56 SD ( $P \leq 0.0001$ ) relative to children of average stature. Additionally, mean AGV from baseline was 5.87 cm/year (95%

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confidence interval 5.14–6.60), resulting in a significant increase of +1.62 cm/year ( $P \leq 0.0001$ ). Injection site reactions were the most common adverse drug reaction observed ( $n = 14$ ); no serious adverse drug reactions were reported. There were no discontinuations due to adverse drug reactions.

**Conclusion:** Vosoritide showed long-term effectiveness in a real-world Portuguese population of patients with achondroplasia. Vosoritide was also well tolerated, and patients showed good adherence to treatment. These findings were consistent with the outcomes of clinical trials and existing real-world experience.

**Keywords:** Achondroplasia; Compliance; Growth; Proportionality; Real-world experience; Safety; Vosoritide

### Key Summary Points

#### *Why carry out this study?*

There is limited evidence to date demonstrating the safety and effectiveness of vosoritide in children with achondroplasia in a real-world setting.

This study evaluated growth, safety, and treatment compliance in children with achondroplasia ( $n = 27$ ) receiving vosoritide at a single Portuguese clinic.

#### *What was learned from the study?*

After 24 months of vosoritide treatment, improvements were observed in height standard deviation score and annualized growth velocity in children with achondroplasia, consistent with clinical trial outcomes and existing real-world evidence.

Vosoritide was well tolerated, and patients showed good adherence to treatment, with no discontinuations due to adverse drug reactions; the most common adverse drug reactions observed were injection site reactions ( $n = 14$ ) and hypertrichosis ( $n = 4$ ).

The preliminary findings of this study contribute to the growing body of evidence supporting the safety and effectiveness of vosoritide in achondroplasia; longer-term follow-up is ongoing.

## INTRODUCTION

Achondroplasia is the most common form of skeletal dysplasia, affecting over 360,000 individuals worldwide [1]. It is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene, leading to overactive *FGFR3* signaling and, thus, inhibition of chondrocyte proliferation and differentiation [2]. Consequently, endochondral bone growth is impaired in affected individuals, resulting in disproportionately short stature [3]. Other characteristic features of achondroplasia include macrocephaly with frontal bossing,

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midface hypoplasia, and genu varum [3–5]. Individuals with achondroplasia may experience a variety of medical, functional, and psychosocial challenges requiring lifelong management by a multidisciplinary team [1]. Complications associated with the condition include foramen magnum stenosis, sleep apnea, recurrent otitis media, spinal stenosis, and obesity [6].

Historically, treatment options for achondroplasia were limited and focused on managing disease symptoms, such as ameliorating body disproportion through limb lengthening. However, this procedure is complex, time consuming, and is often associated with complications [1, 7, 8]. Despite only being approved in Japan, human growth hormone was also used off-label in certain countries, with limited efficacy [9–11].

Vosoritide, a C-type natriuretic peptide (CNP) analog, is currently the only approved treatment that targets the underlying pathophysiology of achondroplasia. CNP is a potent stimulator of endochondral bone growth. Vosoritide has been engineered to resist degradation, thereby increasing its half-life, and works by counteracting overactive FGFR3 signaling to stimulate endochondral bone growth [12, 13].

In August 2021, the European Medicines Agency (EMA) approved vosoritide (daily subcutaneous injection, 15 µg/kg) for use in children with achondroplasia aged ≥ 2 years with open epiphyses based on positive data from an extensive clinical trial program. In October 2023, the EMA approved expansion of the indication to children with achondroplasia aged ≥ 4 months [12–14]. Data from phase 2 and 3 trials, and open-label extensions in children with achondroplasia have demonstrated sustained increases in absolute height gain, annualized growth velocity (AGV), and height standard deviation score (SDS) with vosoritide for up to 7 years [15–23]. Decreases in upper to lower body segment ratio have also been observed over time [17, 24]. Additionally, vosoritide was well tolerated across clinical trials; the most common adverse events were mild and transient injection site reactions [15–17, 22].

Following EMA approval of vosoritide, it is important to share experiences of using vosoritide in the clinic to facilitate a better understanding of its safety and effectiveness in a real-world

setting. This retrospective cohort study aimed to evaluate growth parameters, safety, and treatment compliance in children with achondroplasia receiving vosoritide under an early access program in Portugal. The program was approved in December 2021.

## METHODS

### Study Design, Participants, and Follow-up

Hospitals in Portugal have been using a vosoritide monitoring protocol adapted from the French early access program [25], while also consulting published practical considerations for clinical practice (which provide expert guidance for the use of vosoritide in a real-world setting, including treatment initiation, clinical assessments, treatment response, and follow-up) [26, 27]. In this study, children aged 2–14 years with a genetically confirmed clinical diagnosis of achondroplasia who were treated with vosoritide at Hospital Pediátrico de Coimbra, Portugal for at least 6 months between January 2022 and June 2024 were included. All data were collected retrospectively by medical record analysis. The study was conducted in accordance with the Declaration of Helsinki, and approval from Unidade Local de Saúde de Coimbra ethics committee was obtained (ref. OBS.SF.140-2022; no. 490/CE; 1 August, 2024).

Vosoritide was administered as a daily subcutaneous injection at a dose of 15 µg/kg. Baseline parameters, clinical characteristics, and historical anthropometric measurements were recorded on the first day of vosoritide administration. Patients were followed up at 1, 3, and 6 months, and at 6-monthly intervals thereafter. Physical assessments, blood analysis, and electrocardiograms (ECGs) were conducted at baseline and month 3. Detailed anthropometric measurements and Tanner stage were collected at baseline and every 6 months thereafter; measurements were performed by the same two trained nurses at each visit. Bone age was assessed at baseline and every 12 months thereafter. The safety and tolerability of vosoritide was recorded at each follow-up visit.

## Study Outcomes

The following anthropometric measurements were collected to characterize the effect of vosoritide on growth: standing height (or supine length), height SDS, and AGV. Arm span, sitting height (or crown–rump length), sitting height to height ratio, upper to lower segment ratio were also recorded to assess vosoritide's impact on body disproportion. Other measurements, including leg length, hand length, weight, body mass index, and head circumference, were also collected but not included in this study. Safety and tolerability endpoints included adverse drug reactions and treatment adherence (pauses in or discontinuation of vosoritide).

## Statistical Analysis

All data analysis was performed using R Statistical Software (v4.2.2; R Core Team 2022). Patient characteristics were described as numbers and percent or means and standard deviations (SDs). Standing height was converted to an age- and sex-appropriate SDS value according to a comparison with the reference standards of the World Health Organization (WHO). Growth of the cohort was compared with children from the general population (WHO standard charts) and to an untreated achondroplasia-specific population using one-sample Student's *t* test [4, 28–30]. AGV, which was based on measurements of standing height, was summarized using descriptive statistics, with AGV at the time of vosoritide administration serving as baseline. The minimum time interval used to calculate baseline AGV was 0.42 years. To compensate for deviations in date of anthropometric measurement (e.g., measurements at month 12, which had been taken at 11 months, 20 days) variations were divided by the number of years since treatment initiation to give annual variations. Adverse drug reactions are presented as incidence and percent.

## RESULTS

### Participants

In total, 27 children with achondroplasia (12 girls, 15 boys) were included in the study

(Table 1). Participants were from the following Portuguese regions: North ( $n=13$ ), Center, Lisbon (each  $n=6$ ), Alentejo, Algarve (each  $n=1$ ). Twenty-four participants were White, two participants were Black, and one participant was Asian. Diagnosis was established prenatally in 37.0% of participants and postnatally in 63.0% of participants. In all cases, the *FGFR3* variant occurred de novo. Twenty-one participants had the recurrent *FGFR3* variant c.1138G>A; p.Gly380Arg, and five had c.1138G>C; p.Gly380Arg. The remaining participant, an 8-year-old girl, had the *FGFR3* variant c.1620C>A; p.Asn540Lys, which is more frequently associated with hypochondroplasia [31]. However, as a result of the participant's clinical phenotype, namely early-onset severe short stature (height SDS  $-4.91$  SD, based on WHO growth curves; 0 SD, based on achondroplasia-specific growth curves), a diagnosis of achondroplasia was considered appropriate.

Considering their medical history, 21 participants had foramen magnum stenosis, of whom seven (25.9%) required decompression surgery. Other achondroplasia-associated complications included ear, nose, and throat problems ( $n=19$ ), obstructive sleep apnea ( $n=15$ ; four patients had ongoing non-invasive ventilation during treatment), persistent kyphosis ( $n=5$ ), genu varum requiring 8-plates ( $n=2$ ), and epilepsy ( $n=2$ ). No individuals were excluded from treatment initiation as a result of the severity of their achondroplasia-related complications.

The mean age at treatment initiation was 7.3 years (range 2.2–14.2 years). All children completed a minimum of 6 months of treatment, 26 (96.3%) completed 12 months, 19 (70.4%) completed 18 months, 15 (55.6%) completed 24 months, and 2 (7.4%) completed 30 months. Of the four patients who started vosoritide aged 12 years or older (Table S1), three discontinued treatment (one at 18 months and two at 24 months). The remaining patient is responding well and is continuing treatment.

### Height Standard Deviation Score

Absolute mean height SDS improved from baseline over time with treatment (Figs. 1, S1, S2). In the overall cohort, mean variation in height

**Table 1** Baseline characteristics

	Total (N=27)	Boys (N=15)	Girls (N=12)
Age, years, <i>n</i> (%)			
2–5	9 (33.3)	7 (46.7)	2 (16.7)
6–9	8 (29.6)	3 (20.0)	5 (41.7)
10–12	6 (22.2)	4 (26.7)	2 (16.7)
13–14	4 (14.8)	1 (6.7)	3 (25.0)
Age at treatment initiation, years			
Mean (SD)	7.3 (4.07)	6.3 (4.33)	8.6 (3.51)
Ethnicity, <i>n</i> (%)			
White	24 (88.9)	14 (93.3)	10 (83.3)
Black	2 (7.4)	1 (6.7)	1 (8.3)
Asian	1 (3.7)	0 (0.0)	1 (8.3)
Genetic variant in <i>FGFR3</i> , <i>n</i> (%)			
c.1138G>A (p.Gly380Arg)	21 (77.7)	14 (93.3)	7 (58.3)
c.1138G>C (p.Gly380Arg)	5 (18.5)	1 (6.7)	4 (33.3)
c.1620C>A (p.Asn540Lys)	1 (3.7)	0 (0.0)	1 (8.3)
Height SDS (WHO)			
Mean (SD)	– 5.08 (0.83)	– 4.84 (0.83)	– 5.39 (0.76)
Height SDS (ACH)			
Mean (SD)	– 0.07 (1.13)	0.14 (1.26)	– 0.33 (0.94)
Foramen magnum stenosis, <i>n</i> (%)			
Yes	21 (77.7)	13 (86.7)	8 (66.7)
No/not evaluated	6 (22.2)	2 (13.3)	4 (33.3)
Foramen magnum stenosis severity, <i>n</i> (%)			
Mild	13 (48.1)	9 (60.0)	4 (33.3)
Moderate	2 (7.4)	1 (6.7)	1 (8.3)
Severe	6 (22.2)	3 (20.0)	3 (25.0)
Foramen magnum decompression, <i>n</i> (%)			
Yes	7 (25.9)	5 (33.3)	2 (16.7)
No	20 (74.1)	10 (66.4)	10 (83.3)

Table 1 continued

	Total (N = 27)	Boys (N = 15)	Girls (N = 12)
Ear, nose, and throat complications, <i>n</i> (%)			
Yes	19 (70.4)	11 (73.3)	8 (66.7)
No	8 (29.6)	4 (26.7)	4 (33.3)
Obstructive sleep apnea, <i>n</i> (%)			
Yes	15 (55.6)	9 (60.0)	6 (50.0)
No	12 (44.4)	6 (40.0)	6 (50.0)
Ongoing non-invasive ventilation, <i>n</i> (%)			
Yes	4 (14.8)	2 (13.3)	2 (16.7)
No	23 (85.2)	13 (86.7)	10 (83.3)
Genu varum requiring 8-plates, <i>n</i> (%)			
Yes	2 (7.4)	0 (0.0)	2 (16.7)
No	25 (92.6)	15 (100.0)	10 (83.3)
Kyphosis, <i>n</i> (%)			
Yes	13 (48.1)	7 (46.7)	6 (50.0)
No	14 (51.9)	8 (53.3)	6 (50.0)
Neurological complications (epilepsy), <i>n</i> (%)			
Yes	2 (7.4)	2 (13.3)	0 (0.0)
No	25 (92.6)	13 (86.7)	0 (0.0)

*ACH* achondroplasia, *FGFR3* gene encoding fibroblast growth factor receptor 3, *SD* standard deviation, *SDS* standard deviation score, *WHO* World Health Organization

SDS significantly increased from baseline by +0.38 SD ( $P \leq 0.001$ ) after 12 months and +0.95 SD ( $P \leq 0.0001$ ) after 24 months of treatment, referenced to the untreated achondroplasia-specific population [4]. When compared with children from the general population using WHO standard charts [29, 30], mean variation in height SDS significantly increased from baseline by +0.21 SD ( $P \leq 0.01$ ) after 12 months and +0.56 SD ( $P \leq 0.0001$ ) after 24 months.

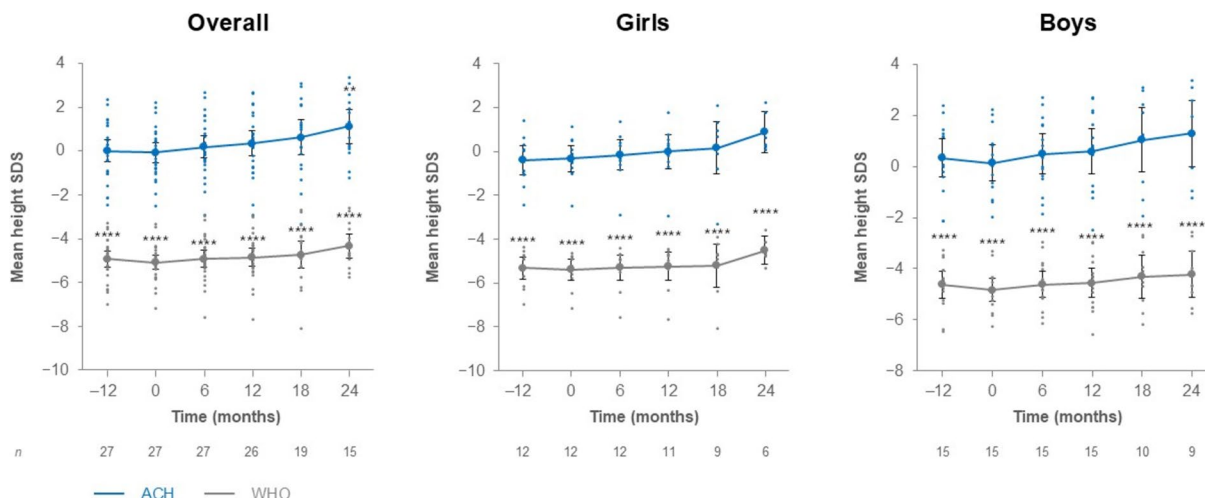
### Standing Height

Vosoritide treatment resulted in improvements in absolute height in children with achondroplasia. Most treated girls surpassed the 50th

percentile on the achondroplasia-specific reference charts, while several boys reached or exceeded the 97th percentile (Fig. 2).

### Annualized Growth Velocity

The overall mean AGV at baseline was 4.25 cm/year (95% confidence interval [CI] 3.58–4.91), which significantly increased to 5.69 cm/year (95% CI 5.02–6.36) after 12 months of vosoritide treatment ( $P \leq 0.0001$ ). After 24 months of treatment, mean AGV was 5.87 cm/year (95% CI 5.13–6.60), resulting in a significant increase of +1.62 cm/year compared with baseline ( $P \leq 0.0001$ ). In girls, mean AGV at

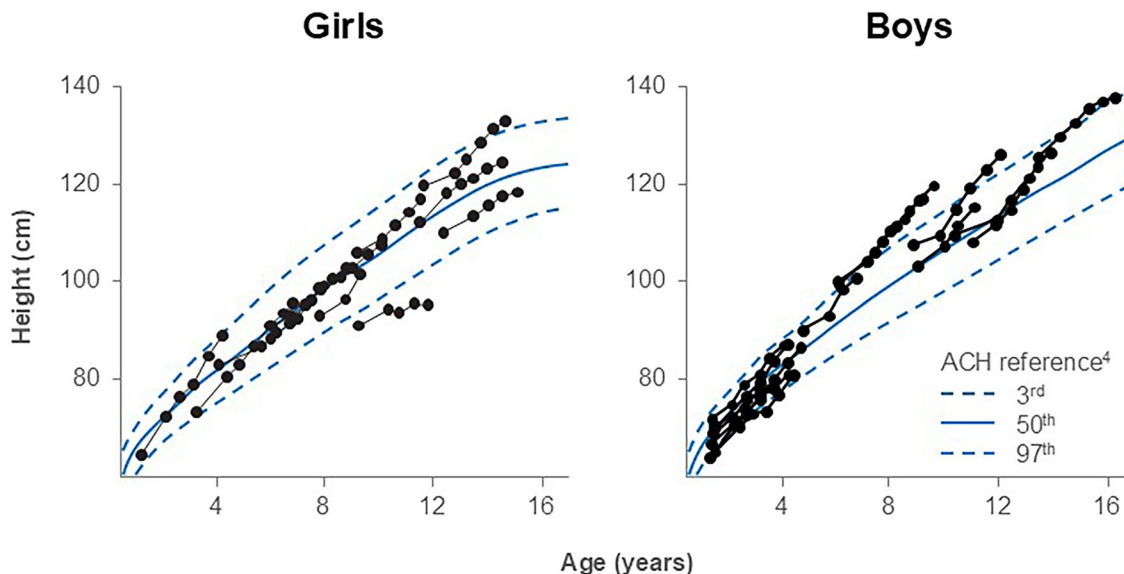


**Fig. 1** Absolute mean height SDS in children ( $n=27$ ) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals.  $**P \leq 0.01$  and  $****P \leq 0.0001$  compared with the ACH or WHO refer-

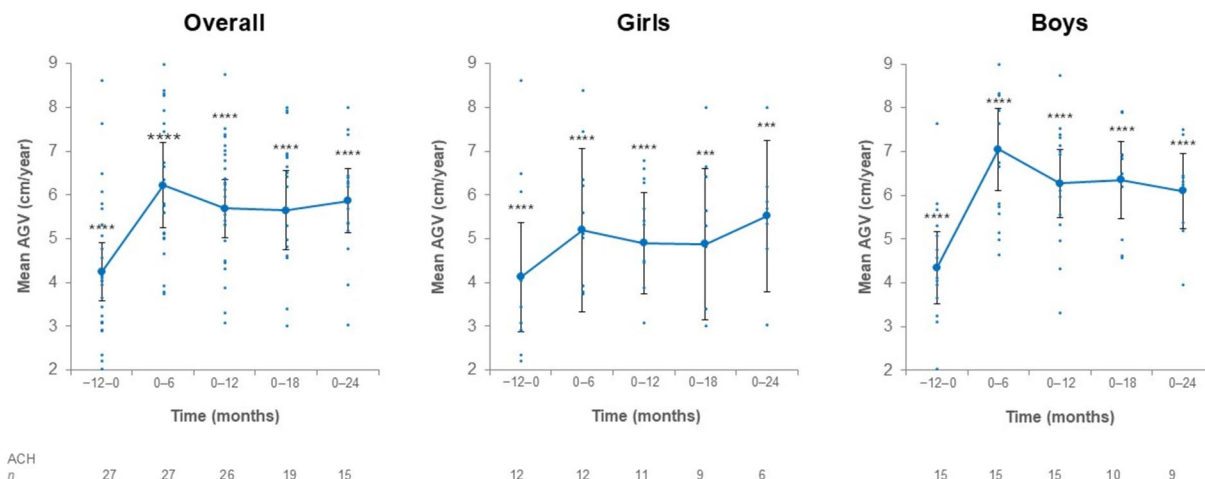
ence growth curves [4, 29, 30]. Individual height SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score, *WHO* World Health Organization

24 months increased by +1.4 cm/year compared with baseline AGV (4.12 cm/year [95% CI 2.89–5.37];  $P \leq 0.001$ ). In boys, mean AGV at 24 months increased by +1.76 cm/year compared with baseline AGV (4.34 cm/year [95% CI 3.52–5.17];  $P \leq 0.001$ ) (Figs 3 and S3). When analyzed by sex, mean variation in height SDS

increased significantly from baseline by +0.85 SD ( $P \leq 0.05$ ) in girls and +1.01 SD ( $P \leq 0.001$ ) in boys at month 24, referenced to the untreated achondroplasia-specific population [4]. Compared with WHO standard growth curves [29, 30], mean variation in height SDS increased significantly from baseline by +0.56 SD ( $P \leq 0.05$ )

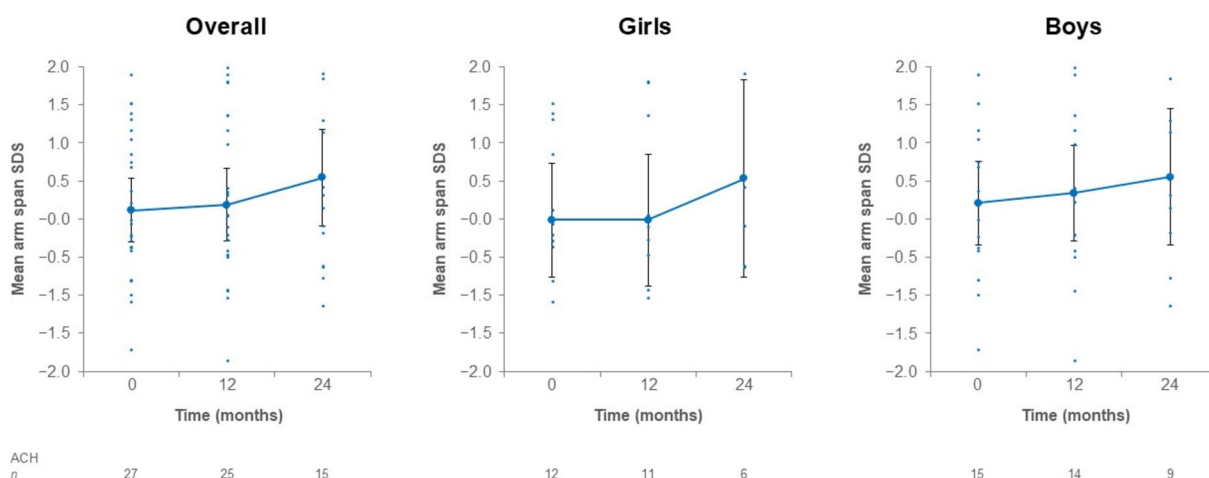


**Fig. 2** Individual height variation following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [4]. *ACH* achondroplasia



**Fig. 3** Absolute mean AGV in children ( $n = 27$ ) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals; the ranges on the x-axis represent the time points between which AGV was calculated.

\*\*\* $P \leq 0.001$ ; \*\*\*\* $P \leq 0.0001$ , compared with baseline AGV. Individual AGV values are also plotted. *ACH* achondroplasia, *AGV* annualized growth velocity



**Fig. 4** Absolute mean arm span SDS in children ( $n = 27$ ) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals. Individual arm span SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score

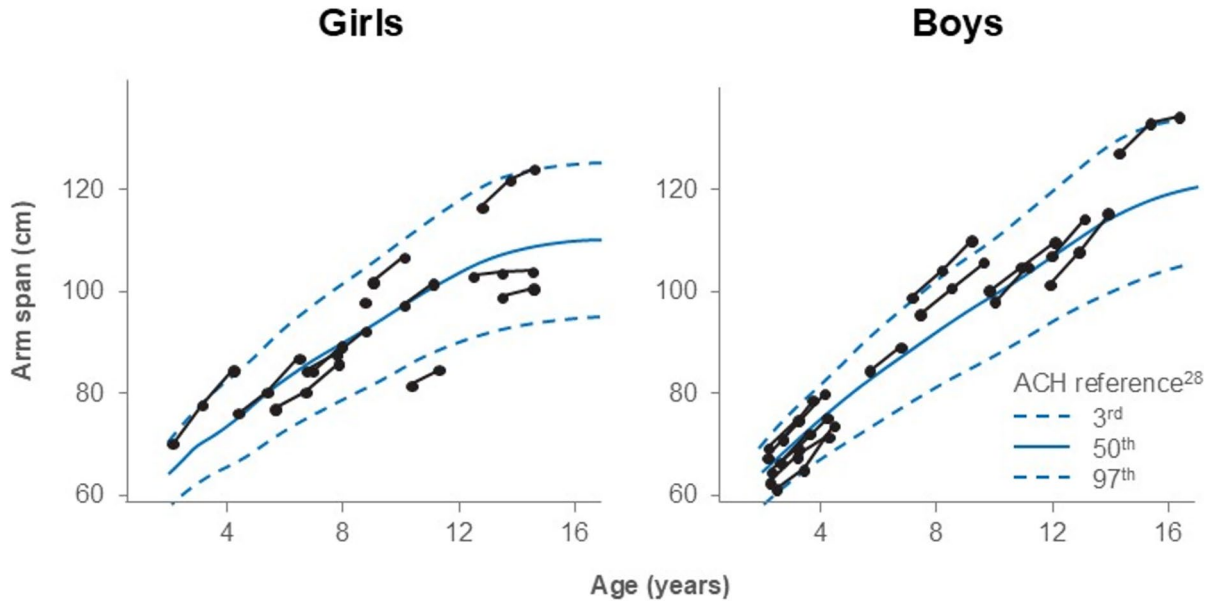
in girls and +0.56 SD ( $P \leq 0.01$ ) in boys after 24 months of treatment.

### Arm Span

Absolute mean arm span SDS, referenced to the untreated achondroplasia-specific population [28], showed an upward trend from baseline to 24 months (Figs. 4 and S4). While this

improvement was not statistically significant overall, there was considerable variability in response between individuals (Fig. 5).

In the overall cohort, mean variation in arm span SDS significantly increased from baseline by +0.13 SD ( $P \leq 0.01$ ) after 12 months of treatment and +0.32 SD ( $P \leq 0.01$ ) after 24 months of treatment compared with the untreated achondroplasia-specific reference population [28]. When analyzed by sex and compared with sex-matched data



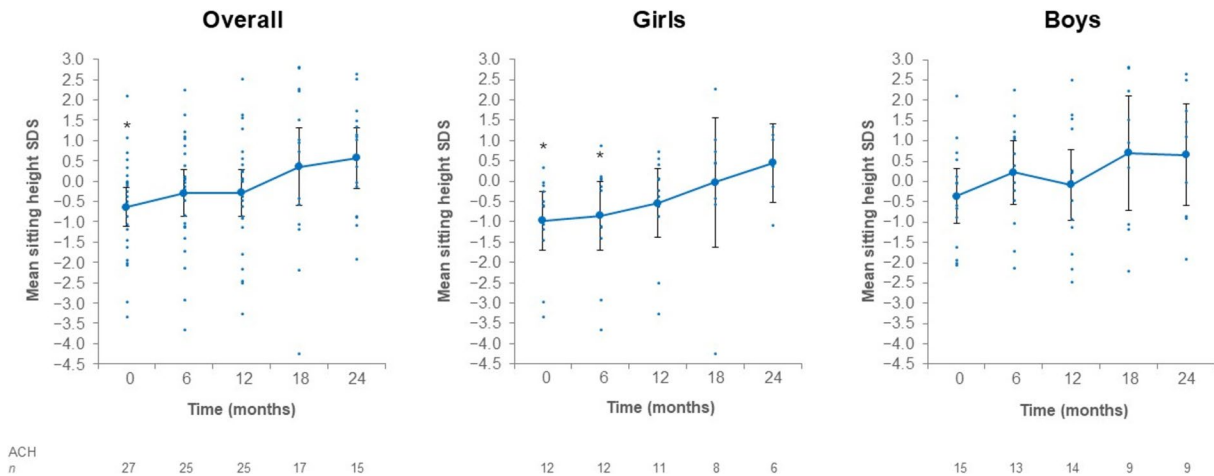
**Fig. 5** Arm span in individual patients following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [28]. *ACH* achondroplasia

from the same reference population, the increase from baseline in mean variation in arm span SDS was significant at 12 months (+0.17 SD;  $P \leq 0.05$ ) and 24 months (+0.38 SD;  $P \leq 0.05$ ) among boys. However, in girls, the improvements from baseline following 12 months (+0.08 SD) and 24 months

(+0.24 SD) of vosoritide treatment were not statistically significant.

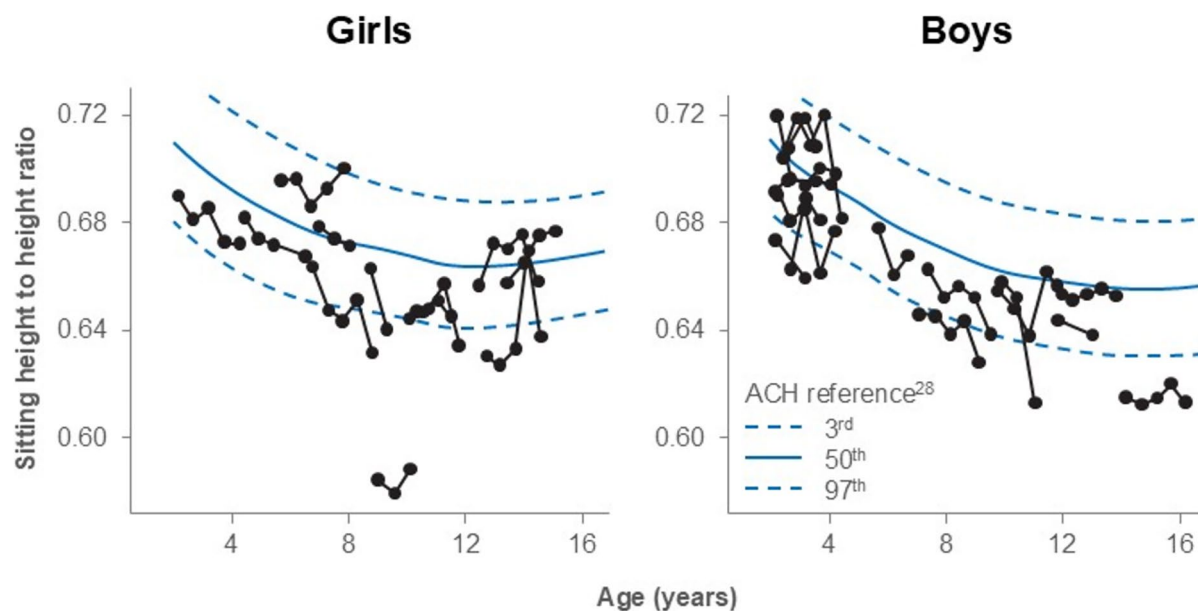
**Sitting Height**

Improvements in absolute sitting height were also observed following vosoritide treatment



**Fig. 6** Absolute mean sitting height SDS in children ( $n = 27$ ) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals. \* $P \leq 0.05$  compared

with the achondroplasia reference growth curve [28]. Individual sitting height SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score



**Fig. 7** Sitting height to height ratio in individual patients following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [28]. *ACH* achondroplasia

(Figs. 6 and S5). In the overall cohort, mean variation in sitting height SDS, referenced to the untreated achondroplasia-specific population [28], significantly increased from baseline by +0.35 SD ( $P \leq 0.01$ ) after 12 months of treatment and +0.79 SD ( $P \leq 0.01$ ) after 24 months of treatment. When analyzed by sex, the increase from baseline in mean variation in sitting height SDS was significant at 12 months among girls (+0.39 SD;  $P \leq 0.01$ ) and 24 months among boys (+0.80 SD;  $P \leq 0.05$ ) compared with sex-matched data from the same reference population.

### Sitting Height to Height Ratio

No statistically significant differences in variation in sitting height to height ratio were observed between baseline and month 24 of vosoritide treatment. Individual sitting height to height ratios are shown in Fig. 7.

### Upper to Lower Segment Ratio

In the overall cohort, there was a significant improvement in mean variation in upper to

lower segment ratio after 24 months of vosoritide treatment ( $-0.10$ ;  $P \leq 0.01$ ). When analyzed by sex, a significant improvement in mean variation in upper to lower segment ratio was observed in boys at month 24 ( $-0.11$ ;  $P \leq 0.05$ ), while no significant improvement was seen in girls. Individual upper to lower segment ratios are shown in Fig. S6.

### Safety and Adherence

Adverse drug reactions were reported by 18 (66.7%) individuals. Injection site reactions, including hematomas, erythema, and local edema, were the most common adverse drug reaction observed ( $n = 14$ ; 51.9%). Other adverse drug reactions were recorded in a limited number of children, including headache, rash, itching, and lipothymia (all  $n = 1$ ; 3.7%). Four patients (14.8%) experienced hypertrichosis, mostly at the dorso-lumbar region (Fig. S7). The time of onset varied in relation to treatment initiation. In all four cases, treatment was continued without interruption, and hypertrichosis stabilized or diminished after a few months. No abnormal blood test results or ECGs were

observed during treatment. One individual had elevated liver transaminases at baseline which did not worsen on treatment. No serious adverse drug reactions were observed.

Throughout the study, there were 29 missed doses of vosoritide reported by nine patients, equating to 0.71 missing doses/patient/year. One patient was responsible for 10 of the 29 missed doses. No patients discontinued treatment because of an adverse drug reaction.

## DISCUSSION

This real-world retrospective cohort study aimed to characterize growth and evaluate safety and tolerability in patients with achondroplasia receiving vosoritide in Portugal. The Bone Dysplasia Multidisciplinary Team at Hospital Pediátrico de Coimbra is the most experienced team nationally, following up with approximately 85% of children diagnosed with achondroplasia in Portugal. The study cohort, which included children of all ages, diverse backgrounds, and from all regions of continental Portugal, is representative of the Portuguese population.

According to published reference data from untreated children with achondroplasia, mean height SDS is  $-2.5$  in girls aged  $<1$  year and  $-3.2$  in boys aged  $<1$  year, compared with age- and sex-matched average-stature children. It decreases to  $-5.3$  SDS in girls and  $-4.6$  in boys by aged 5 years. Mean AGV is 11.6 cm/year in girls aged  $<1$  year and 14.6 cm/year in boys aged 1 year, which decreases to 7.1 cm/year in girls and 7.4 cm/year in boys at 1 year, before steadily declining to 3.6 cm/year in girls and 3.6 cm/year in boys at 10 years [32]. In our study, vosoritide treatment led to improvements in growth across several parameters, including height SDS and AGV, while maintaining an acceptable safety and tolerability profile. Increases in arm span and sitting height were also observed on treatment. Growth acceleration became more apparent over time, with some individuals only showing noticeable effects after 18 months of

treatment. The most substantial improvements were observed at 24 months.

The effectiveness data from our study are concordant with efficacy data from clinical trials with vosoritide. In a phase 3 randomized, placebo-controlled, double-blind study (NCT03197766) with an open-label extension (NCT03424018), significant improvements were observed in absolute height, AGV ( $+1.57$  cm/year;  $P<0.0001$ ), and height SDS ( $+0.28$  SD after 1 year of treatment and  $+0.44$  SD after 2 years of treatment, relative to children of average stature) [16, 17, 23]. These improvements were sustained for up to 4 years [19, 23]. In a phase 2 randomized, placebo-controlled, double-blind study (NCT02055157) with an open-label extension (NCT02724228), vosoritide treatment was associated with increases in AGV in children aged  $\geq 5$  years [15]. An increase in mean (SD) height SDS of  $+1.02$  SD (0.64), referenced to an untreated achondroplasia population, was also observed. Improvements were maintained for up to 7 years [15, 18, 20]. In a separate phase 2 randomized, placebo-controlled, double-blind study in infants and toddlers (NCT03583697) with an open-label extension (NCT03989947), children aged  $\geq 2$  years ( $n=9$ ) treated with vosoritide for 4 years achieved 90.45% of the height of children of average stature, while those aged  $<2$  years ( $n=14$ ) treated for 3 years reached 80.02% of the height of children of average stature [21].

While vosoritide had a positive effect on absolute arm span and sitting height in the present study, its impact was not statistically significant, and considerable variability was observed between individuals. These data should be interpreted in the context of the small sample size, limited follow-up period to date, and the interpatient variability observed, particularly in sitting height. It should also be noted that the effect of vosoritide on arm span and sitting height has not been described extensively in previous studies. To further characterize vosoritide's effect on proportionality, we determined the sitting height to height ratio, which is considered an accurate method of evaluating body proportionality [33–35]. In infants of average stature, sitting height accounts for approximately

two-thirds of their total height, decreasing to approximately 50% of standing height by adolescence [33]. In children with achondroplasia, the median ratio at birth is 0.73, which reduces to only 0.66 at adolescence [36]. In our study, while we observed no significant improvements in sitting height to height ratio between baseline and 24 months overall, some individual patients showed positive responses to vosoritide when compared with the untreated achondroplasia reference population, and this parameter is worthy of further investigation with a longer follow-up.

Clinical trials have typically used upper to lower body segment ratio to evaluate vosoritide's effects on proportionality, a ratio that should be in accordance to sitting height to height ratio. In children of average stature, the ratio of upper to lower body segments is 1.4 at birth, decreasing to 1.0 by 10 years of age as the long bones lengthen relative to the trunk. In children with achondroplasia, the median ratio at birth is 2.0, which reduces to only 1.7 at skeletal maturity [37]. In a phase 3 clinical trial (NCT03197766) with an open-label extension (NCT03424018), vosoritide treatment for up to 2 years led to a mean change from baseline in upper to lower body segment ratio of  $-0.05$  (95% CI  $-0.09$  to  $-0.01$ ) in children with achondroplasia aged  $<12$  years, representing an improvement in proportionality [17]. In our study, significant improvements in mean variation in upper to lower segment ratio were observed in the overall cohort after 24 months of vosoritide treatment (despite seeing no increase in sitting height to height ratio). However, no achondroplasia-specific reference data are available for comparison.

The effectiveness of vosoritide observed in our study was also consistent with real-world data published to date. In the published results from the French early access program, which served as a model for our study design, data were collected from 57 vosoritide-treated children with achondroplasia aged  $\geq 5$  years, across six referral centers [25]. In the 17 participants with 18 months of follow-up, mean absolute height increased by 8.8 cm and mean height SDS improved by 0.56 SD, referenced to an untreated American achondroplasia population [38]. Preliminary data have also been published from a cohort of patients

with achondroplasia ( $n=30$ ) treated with vosoritide for at least 6 months at IRCCS Giannina Gaslini, Genoa, Italy [39]. As with our study, an increase in height SDS was reported. However, the Italian analysis also documented improvements in additional anthropometric parameters following vosoritide treatment, including weight SDS and upper to lower body segment ratio. Data from children with achondroplasia treated with vosoritide across 30 European centers ( $n=236$ ) are also being collected as part of the CrescNet registry at the University of Leipzig [40]. Using the European reference cohort [4], an increase of 1.15 SD in mean height SDS was recorded among patients who had been treated with vosoritide for 24 months. In a retrospective observational study, 34 patients with achondroplasia who received vosoritide for at least 12 months at University Hospital Cologne, Germany, were included in the analysis. When referenced to both achondroplasia and average-stature populations, significant increases in height SDS were observed after 12 months of treatment ( $+0.35$  SD and  $+0.38$ , respectively; both  $P<0.0001$ ). AGV exceeded reference values for untreated children with achondroplasia. However, as in our study, no significant differences were seen in sitting height to height ratio [41].

Vosoritide has been well tolerated in clinical trials conducted to date and its safety profile in children aged  $<5$  years is consistent with that in children aged  $\geq 5$  years [19, 21]. Similar to our observations, in both clinical trials and previous real-world studies, the most common adverse events were mild and largely limited to transient injection site reactions [15–17, 22, 25, 39, 42]. Hypertrichosis was not identified as an adverse event in clinical trials, but several clinical centers have reported cases following vosoritide use in a real-world setting. In July 2024, hypertrichosis was added to vosoritide's Summary of Product Characteristics as an uncommon adverse reaction in treated patients [43]. In our study, four patients (14.8%) experienced hypertrichosis but in all cases treatment was continued without interruption, and hypertrichosis stabilized or resolved after a few months.

Existing real-world studies have reported no instances of treatment discontinuations, interruptions, or missed doses, although this should

be interpreted in the context of the limited follow-up period [25, 39, 42]. We observed infrequent missed doses (approximately 0.71 per patient per year), and no discontinuations due to adverse drug reactions.

Of the four individuals (three girls, one boy) who started vosoritide aged 12 years or older, three discontinued treatment. In two girls, no significant response was observed. In the male patient, a clear response was seen after 12 months of treatment, but this subsequently diminished at 24 months. Vosoritide should be ceased upon confirmation of no further growth potential, indicated by an AGV of less than 1.5 cm per year and the closure of epiphyses [43]. Although AGV in these individuals was slightly above 1.5 cm per year and they had open growth plates at the time of final treatment, vosoritide was discontinued because of their lack of response expected by the patient/team, progression toward maturity, and/or the burden of daily injections. The remaining female patient is responding well and is continuing treatment.

Among the remainder of our cohort, there were three additional individuals who did not show a clear response to vosoritide. Two boys started vosoritide at 2 years of age and have completed 12 months of treatment with limited response so far. Greater variability in response has been observed in younger children within the cohort, although a later positive response remains possible. The third case was a girl who started vosoritide aged 10 years. Her height worsened from  $-2.50$  SDS at baseline (referenced to the untreated achondroplasia-specific population) to  $-3.29$  SDS following 18 months of treatment; vosoritide discontinuation was therefore being considered. She presented with an acute achondroplasia phenotype, including severe foramen magnum stenosis with neurological sequela and significant kyphosis. Although this case may be an outlier, several individuals in the cohort with limited treatment response also have a more severe achondroplasia phenotype, characterized by a greater degree of short stature and associated complications. Nevertheless, it is difficult to determine factors predicting

treatment response in this cohort because of its small size.

The main strength of the data is their homogeneity; they were collected by the same physicians and nurses at a single Portuguese center throughout the study period. Additionally, a consistent baseline growth pattern was observed within our cohort; minimal variation in height SDS was recorded prior to vosoritide initiation. Unlike in clinical trials, no patients were excluded from treatment initiation and data analysis as a result of the severity of their achondroplasia-associated complications. It should be acknowledged that our study utilized WHO standard curves and a European achondroplasia reference cohort [4, 29, 30], whereas the growth curves used in vosoritide clinical trials were based on Centers for Disease Control and Prevention (CDC) reference data for average stature and an American cohort of individuals with achondroplasia [38, 44]. However, this is unlikely to have impacted on the findings.

The present study had some limitations. The single-center, retrospective design may influence the external validity of the findings. Retrospective analysis limited the time points used for data analysis. Sample sizes were also small ( $n=27$ ), especially when considering treatment duration subgroups (e.g., only six girls completed 24 months of treatment). Careful consideration should be made before drawing conclusions from statistical significance in such small subgroups. Small sample sizes were also the reason we did not compare growth and proportionality by age group, which would have been valuable, given they change over time regardless of treatment status. In addition, assessment of health-related quality of life in children with achondroplasia undergoing treatment with vosoritide was not undertaken. A longer follow-up is ongoing to further assess the safety and effectiveness of vosoritide in a real-world setting.

## CONCLUSION

Vosoritide showed long-term effectiveness in a real-world Portuguese population of patients with achondroplasia. Vosoritide was also well

tolerated, and patients showed good adherence to treatment. These initial findings are consistent with clinical trial data and preliminary real-world data from other centers, contributing to the growing body of evidence supporting the safety and effectiveness of vosoritide in managing achondroplasia. Moving forward, it is crucial that vosoritide treatment and subsequent monitoring is integrated into the multidisciplinary care of patients with achondroplasia. Thorough follow-up by an experienced team is also vital. To determine the potential impact of vosoritide on achondroplasia-associated complications, longer-term data collection from larger cohorts in a real-world setting is required.

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**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

### Declarations

**Conflict of Interest.** Inês Rua has received honoraria for lectures and/or travel support from BioMarin and Ascendis; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, BioMarin, and QED. Isabel Silva has received travel support from BioMarin; and has been an investigator in observational studies for BioMarin. Upon completion of the manuscript, Isabel Silva has changed affiliation to Unidade Local de Saúde de São José, Lisbon, Portugal. Christoph Beger has received support for attending meetings and/or travel from BioMarin. Cristina Gomes has received honoraria for lectures and/or travel support from BioMarin; and has been research nurse in observational studies or clinical trials for Pfizer, Ascendis, BioMarin, and QED. Maria J. Pais has been research nurse in observational studies and/or clinical trials for Pfizer, BioMarin, and QED. Alice Mirante has received honoraria for lectures, advisory boards, and/or travel support from BioMarin; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, and BioMarin. Sérgio B. Sousa has received honoraria for lectures, advisory boards, and/or travel support from BioMarin, Ascendis, and Kiowa Kirin; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, BioMarin, and QED.

**Ethical Approval.** The study was conducted in accordance with the Declaration of Helsinki, and approval from Unidade Local de Saúde de Coimbra ethics committee was obtained (ref. OBS.SF.140-2022; no. 490/CE; 1 August, 2024).

Written consent was obtained for the use of any identifying information.

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# Real-world Outcome of Vosoritide Treatment in Children With Achondroplasia: A 12-month Retrospective Observational Study

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## Abstract

**Context:** Vosoritide is the first approved targeted therapy for achondroplasia (ACH) based on increased annualized growth velocity in clinical trials. The aim of our project was an assessment of the real-world setting and treatment with vosoritide.

**Design:** This was a 12-month, retrospective observational study on an inception cohort of 34 patients with ACH treated with vosoritide.

**Patients and Methods:** Thirty-four patients with ACH (22 males; aged 2.8 to 15.3 years at treatment initiation) who received vosoritide treatment for at least 12 months at a specialized clinic for skeletal dysplasia in childhood were included in the analysis. Auxological measurements at baseline and after 12 months of therapy were converted into disease-specific (ACH) and general population [Centers for Disease Control and Prevention (CDC)] z-scores. Physical function assessed by a 6-minute walk test was converted into z-scores and compared to an unaffected reference cohort.

**Results:** After 12 months of treatment, both ACH and CDC height z-scores showed significant increases, with mean changes (mean  $\pm$  SD) of  $0.52 \pm 0.35$  and  $0.38 \pm 0.44$ , respectively (both  $P < .0001$ ). The annualized growth velocity exceeded reference values for untreated children with ACH. No significant changes were observed in body mass index, upper to lower body segment ratio (sitting height/height), or head circumference. The 6-minute walking distance improved, with z-scores increasing from  $-2.00 \pm 1.12$  to  $-1.39 \pm 1.23$  ( $P = .0215$ ).

**Conclusion:** In a real-world setting, children with ACH showed significant improvements in growth and physical function after 12 months of treatment with vosoritide.

**Key Words:** skeletal dysplasia, FGFR3, CNP-analog, growth, annualized growth velocity

Achondroplasia (ACH) is an autosomal-dominant disorder caused by gain-of-function mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*) [1, 2]. The gain-of-function activates the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, which ultimately causes decreased chondrocyte proliferation and differentiation [3]. This leads to impaired endochondral ossification, resulting in disproportioned short stature and characteristic syndromic stigmata such as macrocephaly and midface hypoplasia. Particularly during childhood and adolescence, there is a risk of clinically significant major complications, including recurrent middle ear infections, conductive hearing loss, foramen magnum stenosis, hydrocephalus internus, spinal stenosis, kyphosis, lordosis, and scoliosis [4]. With an estimated prevalence of 3.7 to 4.6 per 100 000 births, ACH is considered the most common skeletal dysplasia [5, 6]. Treatment of ACH requires multidisciplinary management including pediatric, orthopedic, and neurosurgical assessments and counseling [7-9]. The first targeting drug (vosoritide)

treating the underlying pathophysiology of ACH was approved in 2021. Vosoritide, as a recombinant C-type natriuretic peptide analog, stimulates endochondral ossification by inhibiting the overactive *FGFR3* pathway in ACH [10]. In a phase 3 randomized, double-blind, placebo-controlled trial, children with ACH aged 5 years and older receiving vosoritide showed an increase in annualized growth velocity of 1.57 cm/year [11]. Based on data derived from initial studies that investigated selected patient cohorts, vosoritide was recently approved by the US Food and Drug Administration for children of all ages and by the European Medicines Agency for children over the age of 4 months. However, long-term results and real-world data regarding growth, safety, and ACH-related complications are still limited [12-15].

It is still unclear whether data from clinical trials can be directly applied to a patient cohort treated within the label of the drug but without the inclusion and exclusion criteria of a clinical trial. Therefore, we assessed retrospectively the effect of vosoritide in all children treated so far at our center. This

observational study addresses the need for real-life data on the growth of children with ACH aged  $\geq 2$  to  $<16$  years treated with vosoritide over a 12-month period and investigates our hypothesis that the annualized growth velocity would be similar to that observed in the phase 3 trial.

## Patients and Methods

This is a retrospective analysis of all patients with ACH who received vosoritide treatment for at least 12 months at the specialized clinic for skeletal dysplasia of University Hospital Cologne, Germany, between October 2021 and May 2024. Each patient received daily subcutaneous injections of vosoritide at a weight-dependent dose according to the product information [16]. Data were systematically collected during clinical follow-ups at the initiation of therapy; at week 4; and at months 3, 6, 9, and 12 and were prospectively entered into a monocentric disease-specific registry. By June 2024, the registry included data on 56 patients, of whom 34 (12 female, 22 male) had completed at least 12 months of treatment. None of these 34 patients participated in formal National Clinical Trial-registered clinical trials during the observational period. The cohort of 34 patients was categorized into 3 subgroups according to age at therapy initiation ( $\geq 2$  to  $<5$  years,  $\geq 5$  to  $<10$  years, and  $\geq 10$  to  $<16$  years) and 2 subgroups according to sex (male, female).

The primary objective was to assess differences in annualized growth velocity by comparing the cohort and its subgroups with age-, sex- and disease-specific reference values by Savarirayan et al [17] using z-scores. Annualized growth velocity was determined by calculating the ratio of height change (in cm) to the precise number of days between the baseline and 12-month measurements, normalized to a 365.25-day year. These values were subsequently converted to age-, sex-, and disease-specific z-scores by subtracting the reference mean and dividing by the SD provided in the reference dataset [17]. Secondary objectives were to investigate changes in z-scores for height, weight, sitting height/height ratio, and head circumference, as well as changes in 6-minute walking distance, radiological bone age, and quality of life.

Trained nurses conducted the auxological measurements and 6-minute walking tests during clinical visits, ensuring consistency in the methods used throughout the 12-month observation period. Height and sitting height were measured with a stadiometer, weight with a sitting scale, and head circumference standardized with a measuring tape. Z-scores for auxological data were calculated [18, 19] at baseline and at month 12 using the Box-Cox power transformation (L), the median (M), and the coefficient of variation (S) from Center for Disease Control and Preventions (CDC) growth charts [20] and disease-specific growth charts by Merker et al [21, 22]. The CDC growth charts were used in the vosoritide phase 3 trial and were chosen here to maintain consistency and ensure comparability of z-score changes. The ACH growth charts by Merker et al were utilized to assess potential height increases relative to untreated children with ACH. These charts were derived from a European cohort, with most data coming from Sweden and Germany, and thus provided a suitable reference group.

The 6-minute walking distance was measured on a standardized flat-floor course during clinical follow-ups at baseline and months 6 and 12. Z-scores for the 6-minute walking distance were calculated for baseline and month-12 data using reference means and SDs from an unaffected cohort [23].

Radiographic imaging of the left hand was performed at baseline and at month 12 to determine bone age using the Greulich and Pyle method. The change in bone age over 12 months was assessed by subtracting the individual bone age at baseline from the bone age at month 12, followed by calculating the mean change across participants. Additionally, the ratio of bone age to chronological age was calculated. In cases where an exact bone age could not be determined due to dissociated maturation of the carpal bones, the progress of bone age in the different carpal bones during the 12-month observational period was assessed.

Quality of life was assessed using the KIDSCREEN-52 questionnaire, completed by both patients and their caregivers. This questionnaire, designed for children aged 8 and older, consists of 52 items across 10 dimensions: Physical Well-Being, Psychological Well-Being, Moods and Emotions, Self-Perception, Autonomy, Parent Relations and Home Life, Financial Resources, Peers and Social Support, School Environment, and Bullying. The last 4 dimensions were primarily applicable to older schoolchildren, which led to limited data in these areas. Due to additional missing data in these dimensions that could not be retrieved given the retrospective nature of this study, an analysis of the last 4 dimensions was not appropriate. Therefore, only the first 6 dimensions were evaluated in this analysis. For patients aged 8 years and older and their caregivers, responses were analyzed using standardized scores (T-score) according to the KIDSCREEN-52 manual and compared to international reference data. For patients under 8 years of age and their caregivers, the questionnaire was analyzed using absolute scores, as recommended in the original publications [24-26].

## Statistics

Categorical data from the tables, z-scores, and standardized scores from the quality of life questionnaires were calculated using Excel version 16.87. All statistical analyses and graphical representations were conducted with GraphPad Prism version 10.3.0. For the statistical analysis of auxological data, the 6-minute walking test, and pretreatment vs posttreatment quality of life, only patients with both baseline and 12-month data were included. For the statistical analysis of the cohort's baseline quality of life in comparison to an international mean for unaffected children, all children with baseline data were included. The graphical presentation of quality of life over time included all patients, even those with missing baseline or 12-month data.

Normal distribution was tested using the Shapiro-Wilk-Test. For normally distributed data, mean changes were calculated with a 95% confidence interval, and significance was tested using paired *t*-test and 1-sample *t*-test, the latter applied to the analysis of annualized growth velocity and baseline quality of life data. For nonnormally distributed data, the Wilcoxon matched pairs signed-rank test was applied. A *P*-value of less than .05 was considered statistically significant. Normally distributed data in Tables 1 and 2 were described as mean values and SD. Nonnormally distributed values presented in Table 2 were expressed as medians and interquartile ranges.

## Results

### Clinical Data

Thirty-four patients with ACH (12 females and 22 males) were included in the analyses. Clinical data for these patients

Table 1. Clinical data at baseline

	≥2 to <5 years	≥5 to <10 years	≥10 to <16 years	Total cohort
<b>Participants, n (%)</b>	7 (20.6)	21 (61.8)	6 (17.6)	34 (100)
Female	3 (8.8)	8 (23.5)	1 (2.9)	12 (35.3)
Male	4 (11.8)	13 (38.2)	5 (14.7)	22 (64.7)
<b>Height, n (%)</b>	6 (18.8)	20 (62.5)	6 (18.8)	32 (100)
Mean [cm] (range)	80.7 (78.3-83.0)	99.9 (85.2-116.5)	112.4 (97.7-121.0)	
ACH z-scores, mean ± SD	0.36 ± 0.88	0.52 ± 1.44	-0.11 ± 1.33	0.37 ± 1.32
CDC z-scores, mean ± SD	-4.58 ± 0.62	-4.81 ± 1.09	-5.22 ± 1.04	-4.84 ± 1.00
<b>Weight, n (%)</b>	7 (21.2)	20 (60.6)	6 (18.2)	33 (100)
Mean [kg] (range)	13.5 (11.2-16.1)	20.3 (14.5-26.1)	29.0 (21.5-36.6)	
ACH z-scores, mean ± SD	0.39 ± 1.13	0.07 ± 0.98	-0.26 ± 0.94	0.08 ± 1.00
<b>BMI, n (%)</b>	6 (18.8)	20 (62.5)	6 (18.8)	32 (100)
Mean [kg/m <sup>2</sup> ] (range)	21.2 (17.5-25.2)	20.4 (15.2-28.6)	22.8 (21.3-25.0)	21.0 (15.2-28.6)
ACH z-scores, mean ± SD	0.32 ± 1.88	-0.36 ± 1.45	-0.23 ± 0.67	-0.21 ± 1.41
<b>Sitting height/height, n (%)</b>	3 (15.0)	13 (65.0)	4 (20.0)	20 (100)
Mean (range)	0.69 (0.69-0.70)	0.65 (0.60-0.69)	0.66 (0.65-0.67)	0.66 (0.60-0.70)
ACH z-scores, mean ± SD	-0.14 ± 0.57	-1.73 ± 2.06	0.21 ± 0.65	-1.10 ± 1.89
<b>Head circumference, n (%)</b>	5 (25.0)	11 (55.0)	4 (20.0)	20 (100)
Mean [cm] (range)	54.4 (52.5-57.0)	56.3 (53.5-59.0)	56.8 (56.0-58.1)	
ACH z-scores, mean ± SD	-0.30 ± 0.71	-0.20 ± 0.84	-0.41 ± 0.31	-0.27 ± 0.71
<b>Ratio of bone age/chronological age, mean ± SD</b>	0.86 ± 0.25 (n = 2)	0.82 ± 0.16 (n = 8)	0.93 ± 0.18 (n = 4)	0.86 ± 0.17 (n = 14)
<b>Patients with ACH-related/growth-affecting surgeries before/during vosoritide treatment, n (male/female)</b>	1 (0/1)	13 (7/6)	3 (3/0)	17 (10/7)
Limb-lengthening surgery, n (male/female)	0	5 (2/3)	0	5 (2/3)
Corrective osteotomy, n (male/female)	0	2 (1/1)	1 (1/0)	3 (2/1)
Foramen magnum decompression, n (male/female)	1 (0/1)	10 (5/5)	1 (1/0)	12 (6/6)
Ventriculoperitoneal shunt surgery, n (male/female)	0	1 (1/0)	1 (1/0)	2 (2/0)
Corrective spinal fusion surgery, n (male/female)	0	0	1 (1/0)	1 (1/0)
<b>General medical conditions, n (male/female)</b>	2 (2/0)	11 (6/5)	0	13 (8/5)
Intermittent low vitamin D levels requiring supplementation, n (male/female)	1 (1/0)	7 (4/3)	0	8 (5/3)
Nephrocalcinosis, n (male/female)	1 (1/0)	0	0	1 (1/0)
Hereditary spherocytosis, n (male/female)	0	1 (1/0)	0	1 (1/0)
Hearing impairment requiring hearing aids, n (male/female)	0	1 (0/1)	0	1 (0/1)
Prematurity, n (male/female)	0	1 (0/1)	0	1 (0/1)

Abbreviations: ACH, achondroplasia; BMI, body mass index; CDC, Centers for Disease Control and Prevention.

are presented in Table 1. All patients showed the same disease-causing mutation in *FGFR3* [c.1138G > A (p.Gly380Arg)]. The mean age at start of therapy was 7.52 years, with the youngest patient being 2.83 years old and the oldest 15.25 years old. The mean bone age/chronological age ratio at baseline was 0.86 ± 0.17 (n = 14), indicating a mean delayed bone age. The mean height z-score at the initiation of therapy was 0.37 ± 1.32 (mean ± SD) for ACH-specific percentiles, respectively -4.84 ± 1.00 for CDC percentiles.

We identified 17 patients who had undergone ACH-related and growth-affecting surgeries before or during the observational period. Of these, 5 patients had previously undergone limb-lengthening surgery prior to starting vosoritide, and 1 of these patients had additional limb lengthening during the observation period. Thirteen patients also presented with other medical conditions, as listed in Table 1. None of the 34 patients discontinued or interrupted the therapy within the 12-month period. However, vosoritide treatment of 1 patient

was discontinued after 15 months, as decided by the family in agreement with the medical team, due to a lack of therapeutic benefit (5.7 years at therapy start, change in height ACH z-score of -0.09 after 12 months, individual annualized growth velocity of 3.17 cm/year, corresponding to a z-score of -0.73) and the patient's individual burden.

### Annualized Growth Velocity

Annualized growth velocity was assessed for 31 out of 34 patients. Two patients were excluded from this analysis due to incomplete data. One patient lacked baseline height measurements, and the other 1 had missing 12-month height data due to a recent limb-lengthening surgery, which prevented the standardized standing height measurement. Additionally, for 1 patient, no age-specific reference values were available, as these were only applicable up to 14 years of age and the patient was already 16 years old. Consequently, these 3 patients

**Table 2. Auxological data at baseline and month 12, mean and median changes after 12 months of therapy, corresponding significance values, and number of patients per subgroup**

	Month 0	Month 12	$\Delta 0-12 \pm$ SD of differences	P-value	n
<b>Height CDC z-scores, mean <math>\pm</math> SD</b>	-4.84 $\pm$ 1.00	-4.46 $\pm$ 1.06	0.38 $\pm$ 0.44	<.0001	32
Female	-4.47 $\pm$ 0.87	-4.13 $\pm$ 0.84	0.34 $\pm$ 0.42	.0218	11
Male	-5.04 $\pm$ 1.03	-4.63 $\pm$ 1.14	0.41 $\pm$ 0.46	.0006	21
$\geq 2$ to <5	-4.58 $\pm$ 0.62	-4.20 $\pm$ 1.00	0.37 $\pm$ 0.50	.1287	6
$\geq 5$ to <10	-4.81 $\pm$ 1.09	-4.43 $\pm$ 1.11	0.37 $\pm$ 0.44	.0012	20
$\geq 10$ to <16	-5.22 $\pm$ 1.04	-4.79 $\pm$ 1.03	0.43 $\pm$ 0.44	.0619	6
Patients with limb-lengthening surgery	-3.37 $\pm$ 0.93	-3.12 $\pm$ 0.81	0.26 $\pm$ 0.21	.0884	4
<b>Height ACH z-scores, mean <math>\pm</math> SD</b>	0.37 $\pm$ 1.32	0.89 $\pm$ 1.37	0.52 $\pm$ 0.35	<.0001	32
Female	0.92 $\pm$ 1.00	1.38 $\pm$ 0.95	0.47 $\pm$ 0.29	.0003	11
Male	0.09 $\pm$ 1.40	0.64 $\pm$ 1.50	0.55 $\pm$ 0.38	<.0001	21
$\geq 2$ to <5, median (IQR) <sup>a</sup>	0.12 (-0.28; 0.84)	0.51 (0.26; 1.55)	0.68 (0.05; 1.03)	.0625	6
$\geq 5$ to <10	0.52 $\pm$ 0.99	0.99 $\pm$ 1.47	0.47 $\pm$ 0.28	<.0001	20
$\geq 10$ to <16	-0.11 $\pm$ 1.33	0.49 $\pm$ 1.31	0.60 $\pm$ 0.37	.0100	6
Patients with limb-lengthening surgery	2.38 $\pm$ 1.10	2.80 $\pm$ 1.03	0.42 $\pm$ 0.25	.0443	4
<b>Weight ACH z-scores, mean <math>\pm</math> SD</b>	0.08 $\pm$ 1.00	0.30 $\pm$ 1.04	0.22 $\pm$ 0.36	.0013	33
Female	0.84 $\pm$ 0.77	1.01 $\pm$ 0.66	0.17 $\pm$ 0.47	.2547	11
Male, median (IQR) <sup>a</sup>	-0.43 (-1.03; 0.37)	-0.31 (-0.93; 0.52)	0.18 (0.06; 0.44)	.0012	22
$\geq 2$ to <5	0.39 $\pm$ 1.13	0.71 $\pm$ 1.25	0.32 $\pm$ 0.41	.0864	7
$\geq 5$ to <10	0.07 $\pm$ 0.98	0.28 $\pm$ 1.01	0.21 $\pm$ 0.37	.0231	20
$\geq 10$ to <16	-0.26 $\pm$ 0.94	-0.10 $\pm$ 0.84	0.16 $\pm$ 0.30	.2382	6
<b>BMI, mean [kg/m<sup>2</sup>] (range)</b>	21.0 (15.2-28.6)	21.2 (15.4-30.5)	NA	NA	32
<b>BMI ACH z-scores, mean <math>\pm</math> SD</b>	-0.21 $\pm$ 1.41	-0.32 $\pm$ 1.36	-0.11 $\pm$ 0.46	.1802	32
Female, median (IQR) <sup>a</sup>	0.82 (-0.64; 1.25)	0.533 (-0.73; 0.85)	-0.09 (-0.59; 0.36)	.4131	11
Male	-0.46 $\pm$ 1.32	-0.58 $\pm$ 1.38	-0.11 $\pm$ 0.39	.1954	21
$\geq 2$ to <5	0.32 $\pm$ 1.88	0.08 $\pm$ 1.88	-0.24 $\pm$ 0.61	.3837	6
$\geq 5$ to <10	-0.36 $\pm$ 1.45	-0.42 $\pm$ 1.39	-0.05 $\pm$ 0.46	.6074	20
$\geq 10$ to <16	-0.23 $\pm$ 0.67	-0.41 $\pm$ 0.61	-0.18 $\pm$ 0.32	.2326	6
<b>Sitting height/height mean, range</b>	0.66 (0.60-0.70)	0.66 (0.61-0.70)	NA	NA	20
<b>Sitting height/height ACH z-scores, median (IQR)<sup>a</sup></b>	-0.38 (-2.60; 0.13)	-0.41 (-1.58; 0.69)	0.30 (-0.18; 0.89)	.1327	20
Female, median (IQR) <sup>a</sup>	-0.49 (-2.95; -0.24)	-0.96 (-1.59; 0.76)	0.52 (-0.59; 1.25)	.3750	7
Male, median (IQR) <sup>a</sup>	-0.08 (-2.58; 0.36)	-0.12 (-1.87; 0.68)	0.22 (-0.15; 0.71)	.2163	13
$\geq 2$ to <5, mean $\pm$ SD	-0.14 $\pm$ 0.57	-0.38 $\pm$ 1.21	-0.24 $\pm$ 1.15	.7497	3
$\geq 5$ to <10, mean $\pm$ SD	-1.73 $\pm$ 2.06	-1.28 $\pm$ 1.99	0.45 $\pm$ 0.64	.0256	13
$\geq 10$ to <16, mean $\pm$ SD	0.21 $\pm$ 0.65	0.31 $\pm$ 0.47	0.10 $\pm$ 0.25	.4817	4
<b>Head circumference ACH z-scores, mean <math>\pm</math> SD</b>	-0.27 $\pm$ 0.71	-0.15 $\pm$ 0.80	0.12 $\pm$ 0.39	.1763	20
Female	-0.36 $\pm$ 0.50	-0.23 $\pm$ 0.89	0.13 $\pm$ 0.59	.5418	8
Male	-0.21 $\pm$ 0.84	-0.09 $\pm$ 0.78	0.12 $\pm$ 0.20	.0719	12
$\geq 2$ to <5	-0.30 $\pm$ 0.71	-0.21 $\pm$ 0.85	0.93 $\pm$ 0.33	.5669	5
$\geq 5$ to <10	-0.20 $\pm$ 0.84	0.96 $\pm$ 0.24	0.09 $\pm$ 0.48	.5656	11
$\geq 10$ to <16	-0.41 $\pm$ 0.31	-0.15 $\pm$ 0.24	0.26 $\pm$ 0.10	.0124	4

Abbreviations: ACH, achondroplasia; BMI, body mass index; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; NA, not applicable.

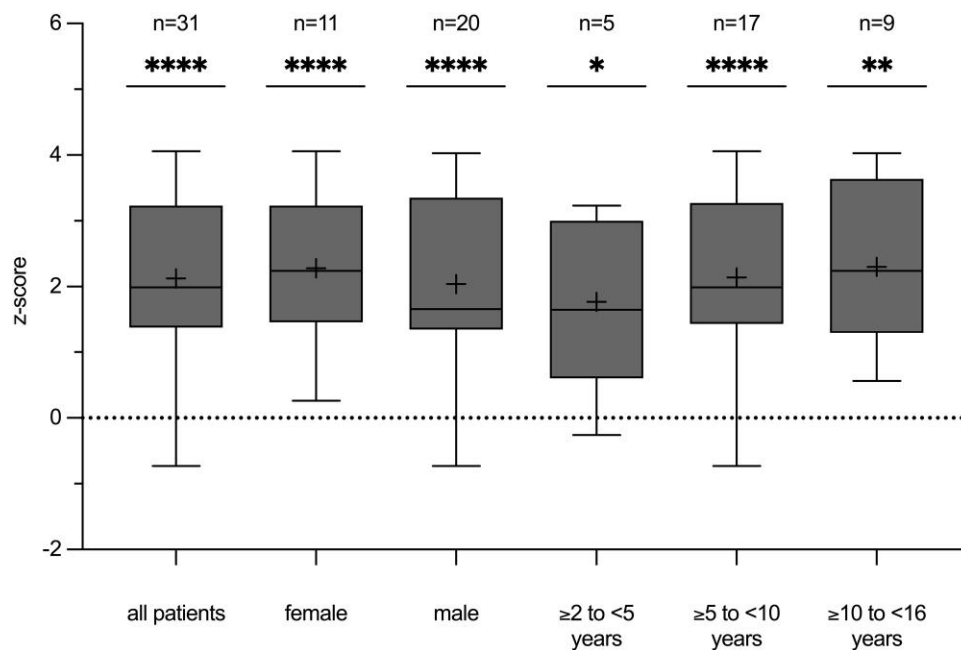
<sup>a</sup>All subgroups were tested for normal distribution using the Shapiro-Wilk test. In this table, normally distributed data is displayed as mean  $\pm$  SD; nonnormally distributed data is displayed as median (IQR). For normally distributed data, significance was tested using paired *t*-test; for nonnormally distributed data, the Wilcoxon matched-pairs signed-rank test was applied.

were excluded from the analyses of annualized growth velocity (but were included in the analysis of other auxological measurements).

Children aged  $\geq 10$  to <16 years ( $n = 5$ ) exhibited the highest mean absolute growth velocity at  $6.98 \pm 1.44$  cm/year, while those aged  $\geq 5$  to <10 years ( $n = 20$ ) showed the lowest at  $5.77 \pm 1.24$  cm/year. Children aged  $\geq 2$  to <5 years ( $n = 6$ ) showed a mean growth velocity of  $6.27 \pm 1.68$  cm/year.

According to sex, females ( $n = 11$ ) exhibited a higher mean absolute growth velocity ( $6.24 \pm 1.04$  cm/year) compared to males ( $n = 20$ ) ( $5.97 \pm 1.56$  cm/year). Patients who had undergone previous limb-lengthening surgeries showed an annualized growth velocity of  $5.55 \pm 0.72$  cm/year ( $n = 4$ ).

Notably, the individual annualized growth velocities were significantly higher compared to age-, sex-, and disease-specific reference values (Fig. 1). The cohort's mean



**Figure 1.** Box and whisker plots of posttreatment growth velocity z-scores. Z-scores were calculated using growth velocity reference values of an untreated achondroplasia cohort [17]. Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (plus symbol), and the Tukey whiskers of the total cohort or of sex-/age-related subgroups. The individual annualized growth velocity was calculated as  $[(\text{height}_2 - \text{height}_1) / (\text{date of measurement}_2 - \text{date of measurement}_1)] / 365.25$  and converted into age-, sex-, and disease-specific z-scores by calculating  $[(\text{individual annualized growth velocity} - \text{annualized growth velocity}_{\text{reference}}) / \text{SD}_{\text{reference}}]$ . Individuals with an annualized growth velocity z-score lower than the reference mean are displayed below zero (dotted line). \* $P \leq .05$ , \*\* $P \leq .01$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ .  $P > .05$  = not significant.

z-score was  $2.13 \pm 1.26$  ( $P < .0001$ ). (The highest z-score was observed in the oldest age group ( $\geq 10$  to  $< 16$  years) at  $2.30 \pm 1.23$  ( $P = .0005$ ), followed by the  $\geq 5$ - to  $< 10$ -year age group at  $2.14 \pm 1.32$  ( $P < .0001$ ) and the  $\geq 2$ - to  $< 5$ -year age group at  $1.77 \pm 1.36$  ( $P = .0434$ ). Annualized growth velocity according to sex revealed a significant z-score increase of  $2.28 \pm 1.14$  ( $P = .0001$ ) in females and of  $2.04 \pm 1.35$  ( $P = .0001$ ) in males. Additionally, patients who had undergone previous limb-lengthening surgeries demonstrated a z-score increase of  $2.67 \pm 1.38$  ( $P = .0304$ ,  $n = 4$ ).

### Changes in Height z-scores

Height measurements from 32 patients were converted into ACH-specific z-scores [21] and CDC z-scores [20] (Fig. 2A and 2B, Table 2). After 12 months of therapy, 29 of the 32 patients demonstrated improvement in their ACH z-score and 26 of the 32 patients showed an increase in CDC z-score. The mean ACH z-score for height after 12 months of therapy was  $0.89 \pm 1.37$ , which was significantly higher ( $P < .0001$ ) than the mean z-score at the start of therapy ( $0.37 \pm 1.32$ ), resulting in a mean change in ACH height z-score of  $0.52 \pm 0.35$ . Similarly, the CDC z-scores showed a significant increase ( $P < .0001$ ) from  $-4.84 \pm 1.00$  to  $-4.46 \pm 1.06$  over the 12-month therapy period, giving a mean change of  $0.38 \pm 0.44$ . Patients who had undergone limb-lengthening surgeries showed a mean change of  $0.42 \pm 0.25$  ( $P = .0443$ ,  $n = 4$ ) in ACH z-score and  $0.26 \pm 0.21$  ( $P = .0884$ ,  $n = 4$ ) in CDC z-score, reflecting a smaller improvement compared to the rest of the cohort.

Despite the positive mean change for the entire cohort, 3 out of 32 patients exhibited a slight decrease in their ACH z-score, with a mean decrease of  $-0.06 \pm 0.03$  after 12 months of therapy.

### Weight, Body Mass Index, Sitting Height/Height Ratio, and Head Circumference

Alongside the increased growth, there was a significant increase ( $P = .0013$ ) in the ACH z-score for weight, from  $0.08 \pm 1.00$  to  $0.30 \pm 1.04$ . However, no significant changes in body mass index or in head circumference or body proportions (sitting height/height) were observed after 12 months of therapy (Fig. 3, Table 2).

### 6-minute Walking Distance

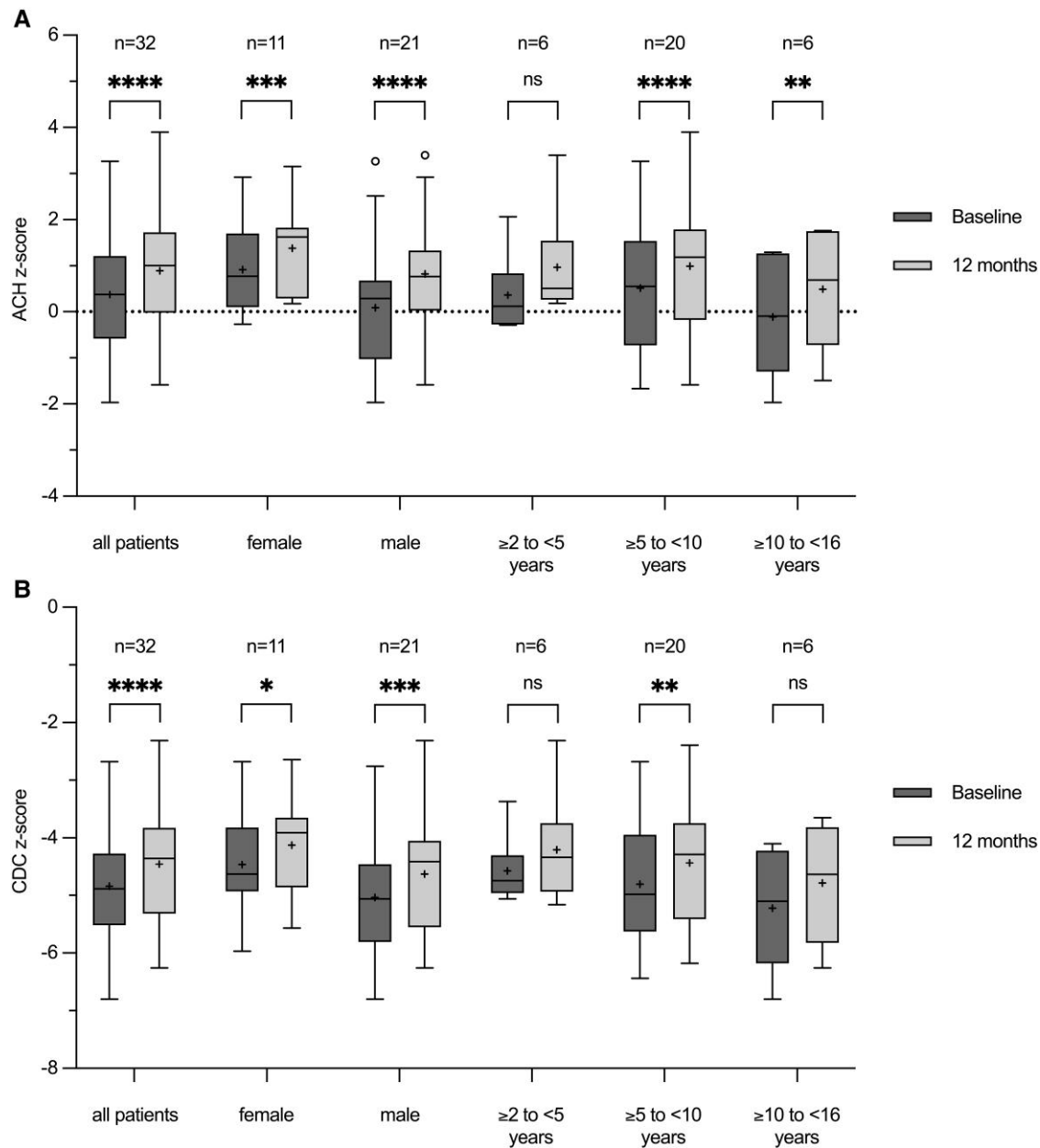
The 6-minute walking distances were converted into z-scores based on age-specific reference values from an unaffected cohort [23]. Aligning with the increased growth in height, a simultaneous notable increase ( $P = .0215$ ) in z-scores for the 6-minute walking distance was observed, improving from  $-2.00 \pm 1.12$  to  $-1.39 \pm 1.23$  (Fig. 4).

### Bone Age

Bone age could be determined for 14 patients at baseline and 12 months. Over the 12-month period, the mean change in bone age was  $1.01 \pm 0.63$  years (mean  $\pm$  SD,  $n = 14$ ). Consistent with this, the bone age to chronological age ratio remained unchanged, with a ratio of  $0.86 \pm 0.17$  at baseline and  $0.86 \pm 0.15$  ( $n = 14$ ) at month 12. For the other patients, an exact bone age could not be determined due to dissociated maturation of the carpal bones. However, manual comparison of the radiographs revealed no signs of accelerated bone maturation during the observational period.

### Quality of Life

Quality of life was assessed using the KIDSCREEN-52 questionnaire, completed by both patients and their caregivers.



**Figure 2.** Box and whisker plots of height z-scores at baseline (darker grey, left) and at month 12 (lighter grey, right). Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (plus symbol), and the Tukey whiskers of the total cohort or of sex-/age-related subgroups. Outliers are represented as circles. Z-scores were calculated using LMS data derived from auxological data of a European cohort with achondroplasia [21, 22] (A) and of an unaffected cohort, the latter provided by the Centers for Disease Control and Prevention [20] (B). \* $P \leq .05$ , \*\* $P \leq .01$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ .  $P > .05$  = not significant.

All available data were graphically represented and analyzed over time. For children aged 8 years and older (and their caregivers), international reference values from an unaffected cohort were available. Interestingly, at the beginning of therapy, children with ACH aged 8 years and older scored significantly above the international mean in the Physical Well-Being dimension (Fig. 5A). Additionally, in the Self-Perception dimension, caregiver responses indicated scores significantly below the international mean, whereas the children's self-reported scores were above the mean, though not significantly (data not shown). Over time, no clear or significant trends were observed in the responses, although there was a slight downward trend in Physical Well-Being, especially in the responses by caregivers

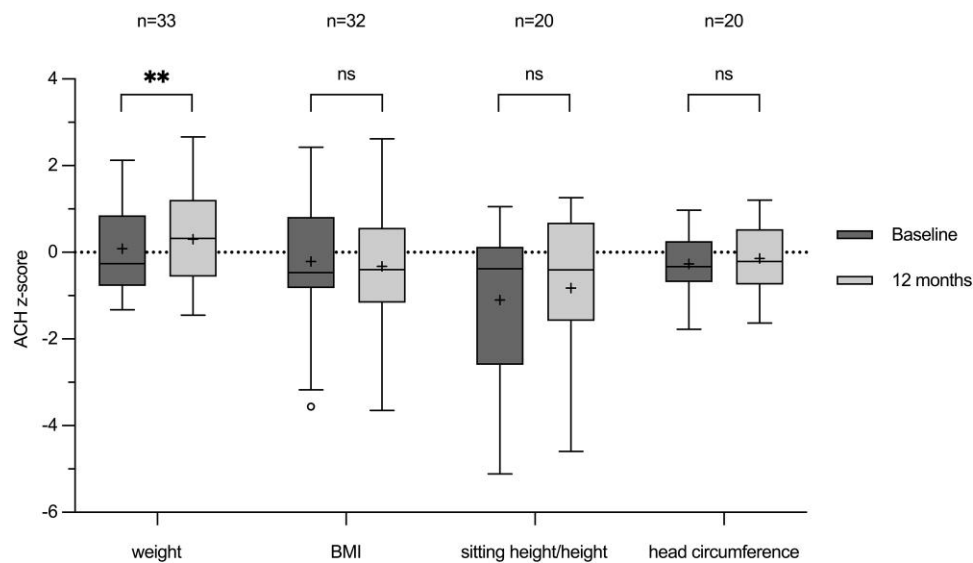
(Fig. 5B). Overall, the trajectories varied widely both between and within individuals.

### Reported Side Effects

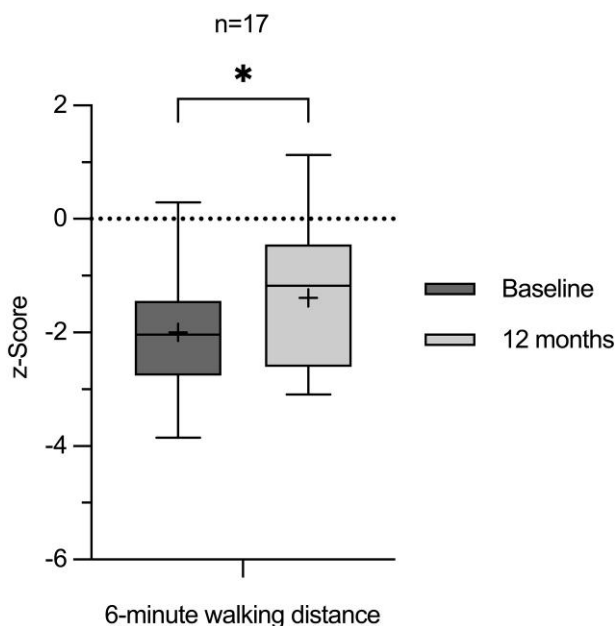
Throughout the 12-month treatment period, 12 of the 34 patients reported mild local injection site reactions as adverse effects. Two patients experienced dizziness as a moderate side effect.

### Discussion

This study evaluated the effects of vosoritide treatment on the growth of children with ACH in a real-world setting.



**Figure 3.** Box and whisker plots of achondroplasia z-scores of body weight, body mass index, sitting height/height and head circumference at baseline (darker grey, left), and at month 12 (lighter grey, right). Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (plus symbol), and the Tukey whiskers of the total cohort or of sex-/age-related subgroups. z-scores were calculated using LMS data derived from auxological data of a European cohort with achondroplasia [21, 22]. \* $P \leq .05$ , \*\* $P \leq .01$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ .  $P > .05$  = not significant.



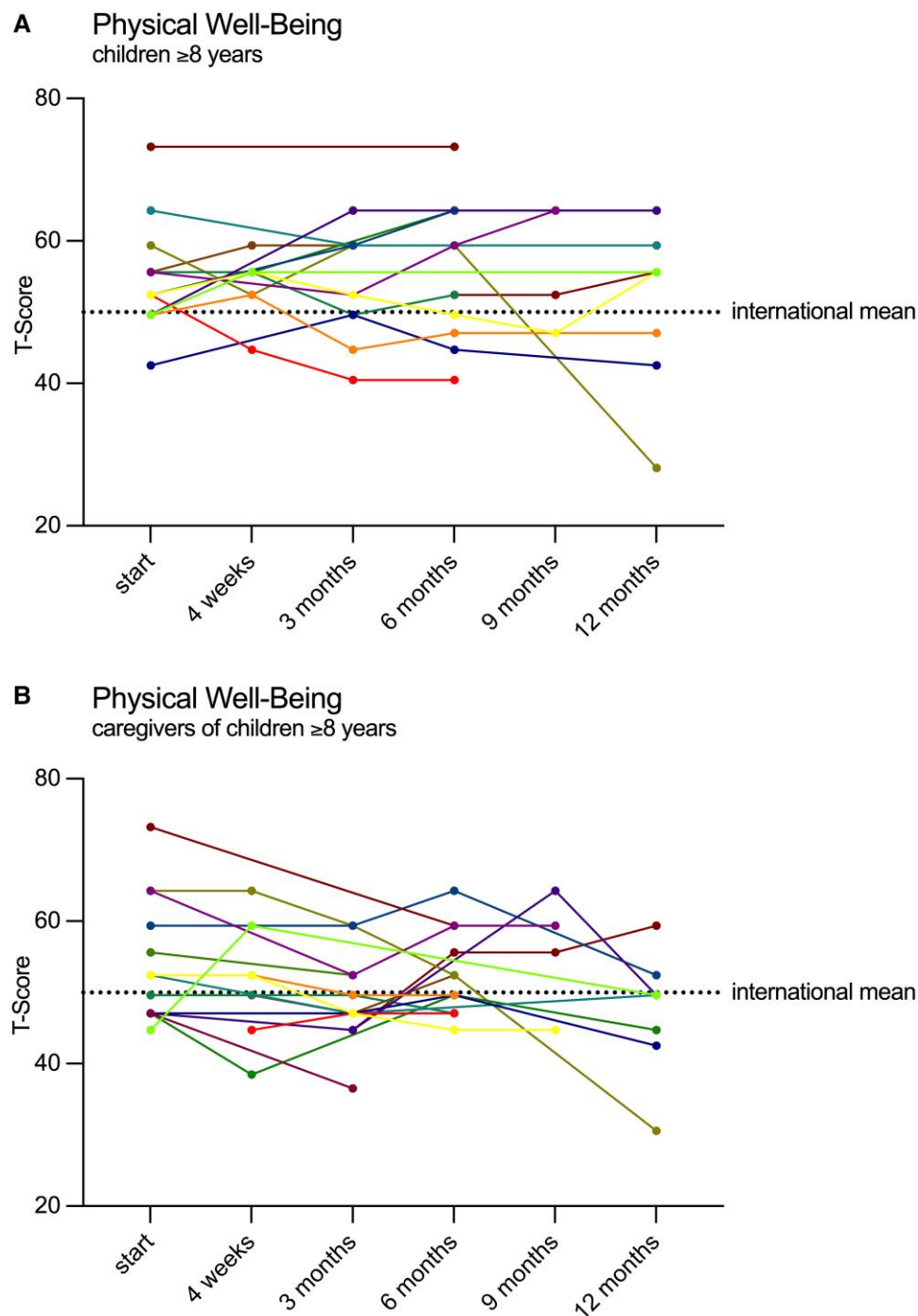
**Figure 4.** Box and whisker plots of z-scores of 6-minute walking test at baseline (darker grey, left) and at month 12 (lighter grey, right). Each box plot displays the 25th and 75th quartiles (box edges), the median (midline), the mean (plus symbol), and the Tukey whiskers of the total cohort or of sex-/age-related subgroups. z-scores were calculated using LMS data derived from auxological data of an unaffected cohort [23]. \* $P \leq .05$ , \*\* $P \leq .01$ , \*\*\* $P \leq .001$ , \*\*\*\* $P \leq .0001$ .  $P > .05$  = not significant.

Consistent with previous findings from a phase 3 trial, which showed an increase in annual growth velocity by 1.57 cm/year compared to individual pretreatment growth velocity, our cohort demonstrated a significant increase in growth, as indicated by improvements in height z-scores. Notably, the patients experienced an increase not only in disease-specific

z-scores but also in CDC z-scores, which are based on growth data of unaffected children. This suggests that treated patients exhibited catch-up growth in comparison to both untreated children with ACH and unaffected children over the 12-month period. Interestingly, the mean improvement of the height CDC z-score in our cohort was  $0.38 \pm 0.44$  and exaggerated the results of the phase 3 trial of vosoritide, where an increase of  $0.24 \pm 0.32$  (mean  $\pm$  SD) in the vosoritide group was observed after 52 weeks of treatment. Furthermore, the annual growth velocity in our cohort was elevated compared to disease-specific reference values. Notably, bone age progressed in accordance with the elapsed time.

As expected, the increased height was also associated with an increase in weight z-scores. At the same time, at least after 12 months of therapy, no significant change in body mass index was observed. Therefore, we have no hint that the increase in weight would lead to additional overweight within this cohort.

Previous studies have shown a positive correlation between increased height and a longer 6-minute walking distance [23]. Therefore, it was not surprising that the increased growth observed in our cohort was also accompanied by a notable increase in the 6-minute walking distance. This increase in walking distance could translate into enhanced physical activity. A recent study has shown that higher levels of physical activity in adult patients with ACH are positively associated with several dimensions of health-related quality of life, particularly general health, vitality, and physical functioning [27]. Overall, patients with ACH have shown lower health-related quality of life and higher psychological distress in adulthood compared to the general population [27]. Therefore, it is important to evaluate quality of life already in children with ACH as a standard component in the multidisciplinary management. Recent published data have revealed that persistent growth-promoting effects of vosoritide in children with ACH are accompanied by improvements in physical and social aspects of health-related quality of life



**Figure 5.** Time course of quality of life in the physical well-being dimension, determined by the KIDSCREEN-52 questionnaire. Responses were given by patients  $\geq 8$  years (A) and their caregivers (B). Each graph represents an individual patient and each dot the response given at that time. Responses were normalized and represented as T-scores according to the KIDSCREEN-52 manual. The dotted line symbols the international mean of an unaffected cohort in this dimension [24-26].

[28]. In contrast to that, we did not observe a significant change in quality of life in our cohort; in fact, there was a slight nonsignificant downward trend in the Physical Well-Being dimension according to caregiver responses. However, the responses regarding quality of life varied widely both between and within individuals, making it difficult to draw clear conclusions about the changes after 12 months of vosoritide treatment. Additionally, one has to keep in mind that Savarirayan et al reported an improvement of quality of life after 3 years of treatment and according to changes

in z-score [28]. Based on that, we will reassess quality of life continuously during treatment with vosoritide.

In line with the findings from the phase 3 trial, our study did not observe changes in the upper to lower segment body ratio. As suggested by Savarirayan et al [11], such changes might only become evident if treatment is initiated at a younger age than in our study and if the observation period extends beyond 12 months. Long-term studies on the effects and side effects of vosoritide treatment are currently ongoing (NCT03424018, NCT02724228, NCT03989947) and will

also assess changes from baseline in body proportion ratios of the extremities as a secondary outcome measurement. Regarding a long-term investigation of vosoritide treatment, it will also be important to examine whether the observed growth acceleration is consistent across multiple years of treatment or diminishes over time, as seen with other pharmacological therapies. For instance, treatment with recombinant GH, which is approved for ACH in Japan, has shown significant catch-up growth during the first 1 to 3 years, which subsequently plateaued after the fourth year [29]. Based on this observation, recombinant GH was never approved for ACH treatment in Europe. Unlike vosoritide, however, GH does not target the pathophysiological mechanisms of ACH.

Importantly, 3 of 32 patients exhibited a decrease in their ACH height z-score. These 3 patients ranged in age from 3.1 to 5.7 years and included 2 males. All were prepubertal and presented with a delayed bone age of more than 1 year. Two patients required cervical decompression in early childhood. One of these patients discontinued treatment with vosoritide after 15 months.

We could not identify any distinguishing characteristics among these 3 children compared to the rest of the cohort that could explain the decrease in height z-scores. It is important to note that, given this was a retrospective analysis, no electronic diary was kept to maintain the daily administration of vosoritide. Routinely, patients and caregivers were asked about missed doses on each visit. Noncompliance with the therapy was not documented in the medical charts of these 3 patients. Considering the burden of the treatment, noncompliance remains a potential contributing factor to the observed treatment failure. Additionally, findings from Hoover-Fong et al suggest a correlation between pretreatment annual growth velocity and the subsequent increase in growth velocity following therapy, with lower baseline growth velocities being associated with greater magnitude of change [30]. In this study, however, there was no pretreatment observation period, preventing the assessment of initial annual growth velocity. Therefore, no conclusions can be drawn regarding these 6 patients that showed a decrease in height z-score.

This study has several limitations. Due to ACH being a rare disease, studies involving patients with ACH are often constrained by small cohort sizes. In this study, the cohort included 34 patients—a relatively large number for a single-center study yet still limited in terms of statistical power. Moreover, the distribution across age groups was uneven. As newer medications are typically administered to older children before younger ones in clinical practice, the number of younger patients in the study was limited. Furthermore, vosoritide treatment is only possible when growth plates are still open, which restricted the inclusion of adolescent patients. Consequently, the numbers of patients in the age groups of  $\geq 2$  to  $< 5$  years and  $\geq 10$  to  $< 16$  years were smaller compared to the middle age group.

Another limitation is that, while the data were prospectively recorded in a registry, the analysis was conducted retrospectively. Therefore, missing data like pretreatment growth velocity, measurements of compliance and assessment of pubertal status could not be retrieved. The lack of baseline growth data limits the ability to directly compare our findings with those from the phase 3 trial of vosoritide. In the phase 3 study, a 6-month observation period prior to therapy allowed for intraindividual comparisons of annual growth velocity before and after treatment. In contrast, our study relied on

comparisons with reference values rather than individual growth rates prior to therapy [31]. Another limitation is the lack of information regarding the effect of vosoritide on surgical procedures. This is an important factor, especially for the long-term treatment in these children.

Nonetheless, this study has strengths as it presents the first real-world data on the use of vosoritide in children with ACH. Due to the fact that it is a single-center study, all measurements were conducted by the same trained staff with long-time experience in measuring children with growth disorders. Assessments were taken based on a standardized protocol at our center and at predefined timepoints during clinical visits. Therefore, the results can be regarded as first proof that effects presented in the phase 3 trial are reproducible in a routine real-world setting, at least in a high-experienced center for children and adolescents with rare skeletal disorders.

In summary, our findings demonstrate that children with ACH show increased growth after 12 months of treatment with vosoritide. Specifically, our cohort exhibited a higher annual growth velocity compared to disease-specific reference values, along with improvements in individual height z-scores. However, no significant effect was observed on the upper to lower segment body ratio, as assessed by the ratio of sitting height to body height after 12 months. Future research should focus on long-term outcomes and assessment of the potential effects on body proportions and comorbidities. Lastly, identifying potential predictive factors for response seems to be essential to reduce the risk of side effects and improve personalized treatment.

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## Author Contributions

S.R. wrote the first draft of the paper. O.S. and H.H.K. designed the study. All data were collected during clinical visits with the support of O.S., S.J.W., S.S., M.R., E.P., and H.H.K. Data analysis was done by S.R. and revised by O.S. and H.H.K. Revision and final approval of the manuscript were done by all authors.

## Disclosures

None of the authors have a conflict of interest influencing this analysis. No funding was received for the study by pharmaceutical companies. O.S., S.J.W., and H.H.K. are investigators in clinical trials investigating the use of vosoritide in different diseases and received honoraria for presentations and consultancies.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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# REAL WORLD EXPERIENCE OF CHILDREN WITH ACHONDROPLASIA WITH VOSORITIDE TREATMENT

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## INTRODUCTION

Achondroplasia is the most common skeletal dysplasia with disproportionate severe short stature, with a prevalence of 0.44 per 10,000 live births in South America. It is characterized by gain-of-function of type 3 fibroblast growth factor receptor (FGFR3) gene in the chondrocytes from the growth plate.<sup>1,2</sup>

In December 2021, a new pharmacological treatment was approved for children with achondroplasia, a modified natriuretic peptide type B, vosoritide. It restores chondrogenesis through the natriuretic peptide receptor B (NPR-B) cellular signaling stimulating inhibition of the overactive RAS signal cascade activated by the mutated FGFR3 gene.<sup>3</sup>

## OBJECTIVE

To assess real world response of children with achondroplasia to treatment with vosoritide.

## METHODS

Twenty-three children (2 - 10 years old) with a genetic confirmed diagnosis of achondroplasia were treated with vosoritide, following the dose regimen described in the product's package insert.<sup>4</sup> Height and weight were measured, and height velocity was calculated after 6 months (n=12) of treatment. Adverse events were monitored in all 23 children. Statistical analysis was performed through Student's t test, with significance level set at  $p < 0.05$ .

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## RESULTS

### Effectiveness

Mean age at start of treatment with vosoritide was 8.16 years (2-10 years). Height velocity prior to treatment was  $3.85 \pm 0.94$  cm/year, mean height velocity SDS (Standard Deviation Score) was  $-2.32 \pm 0.98$ , and mean height SDS (WHO standards) was  $-4.80 \pm 0.67$  (Figure 1). The sitting height to height ratio (SH/H) was elevated (mean  $0.66 \pm 0.02$ ).

After 6 months of treatment, there was a statistically significant difference in mean height velocity and mean height velocity SDS: height velocity increased to  $5.09 \pm 1.5$  cm/year and mean height velocity SDS to  $-0.85 \pm 1.5$  (Figure 1;  $p=0.005$  and  $p=0.023$ , respectively). No significant difference was observed in mean height SDS after 6 months of treatment (Figure 1).

Individual variation is defined as the calculated difference between anthropometric values before and after the intervention ( $\Delta$ ). A positive value indicates a gain, whereas a negative value indicates a loss. As shown in Figure 2,  $\Delta$  height SDS ranged from  $-0.74$  to  $+1.62$ ,  $\Delta$  height velocity from  $-0.98$  to  $+4.09$ , and  $\Delta$  height velocity SDS from  $-1.23$  to  $+5.63$ . SH/H was mostly unchanged, with a mean value of  $0.67 \pm 0.02$ .

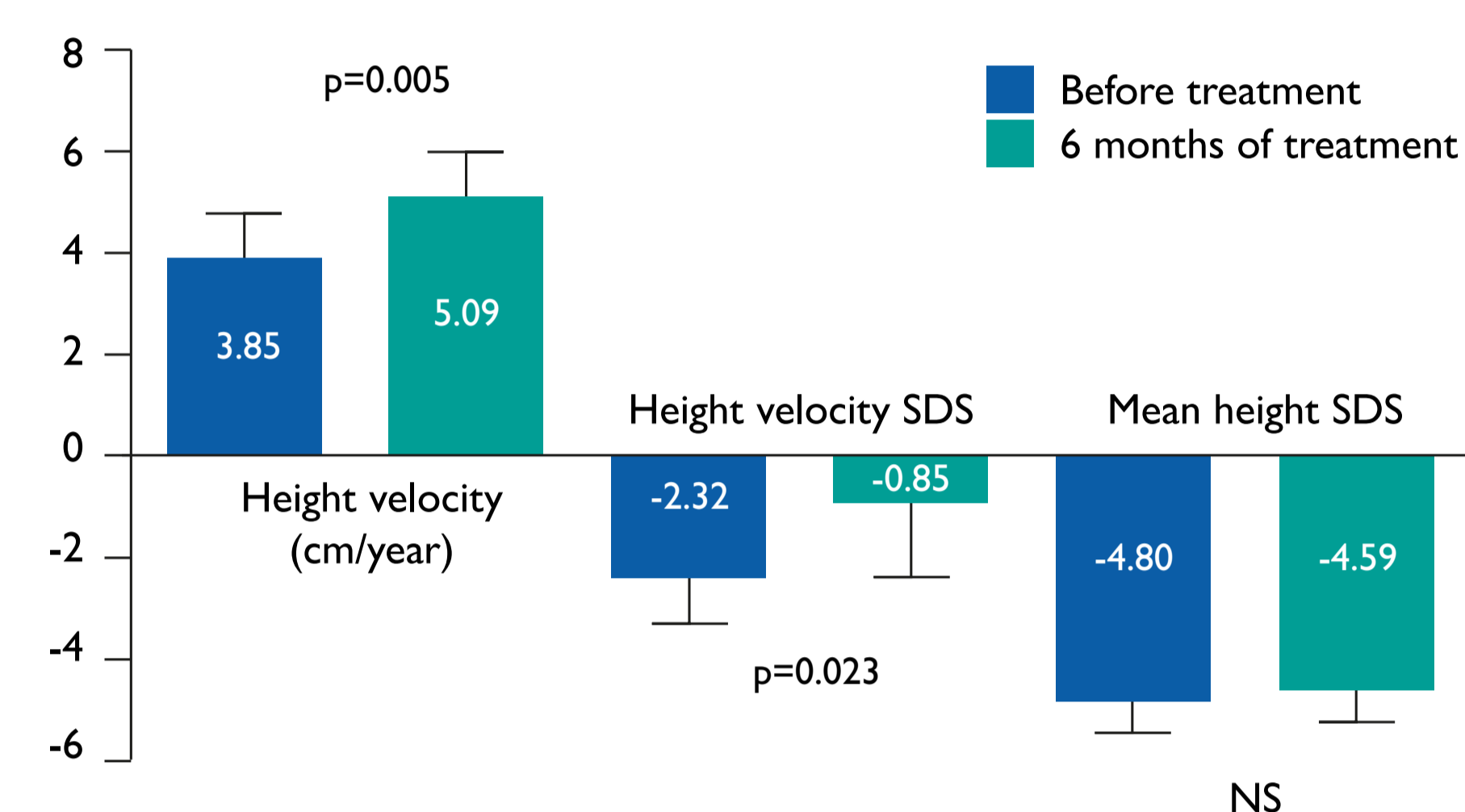
Parents and patients report improvements in the easiness to accomplish daily activities and limb pain (Figure 3).

### Safety

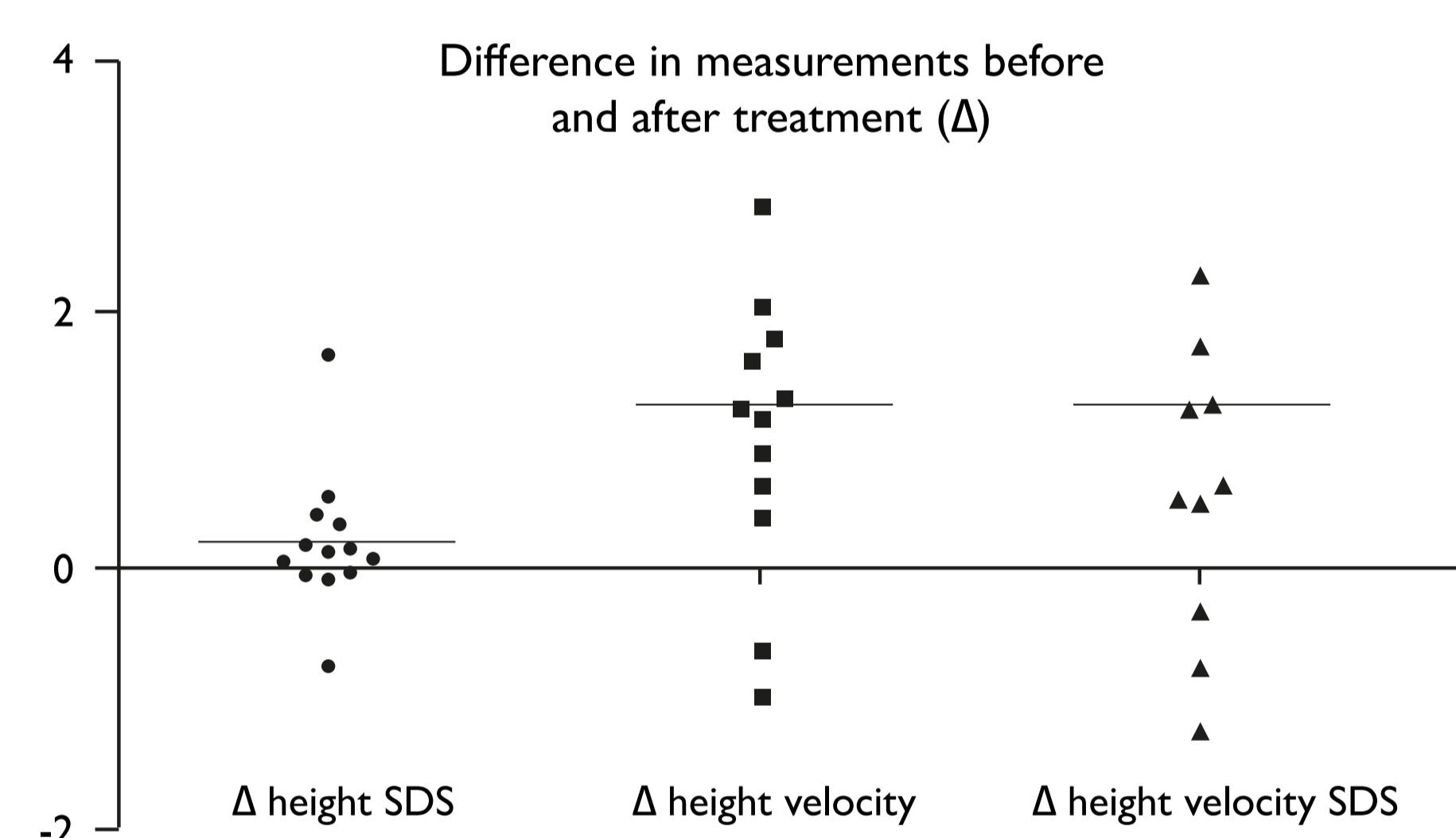
Eight patients presented hypertrichosis (n=7 females and n=1 male; Figure 4); the duration of treatment until the perception of hypertrichosis varied between 3 and 8 months, with a mean duration of  $4.37 \pm 1.99$  months. Three patients reported local pain at injection site.

## CONCLUSION

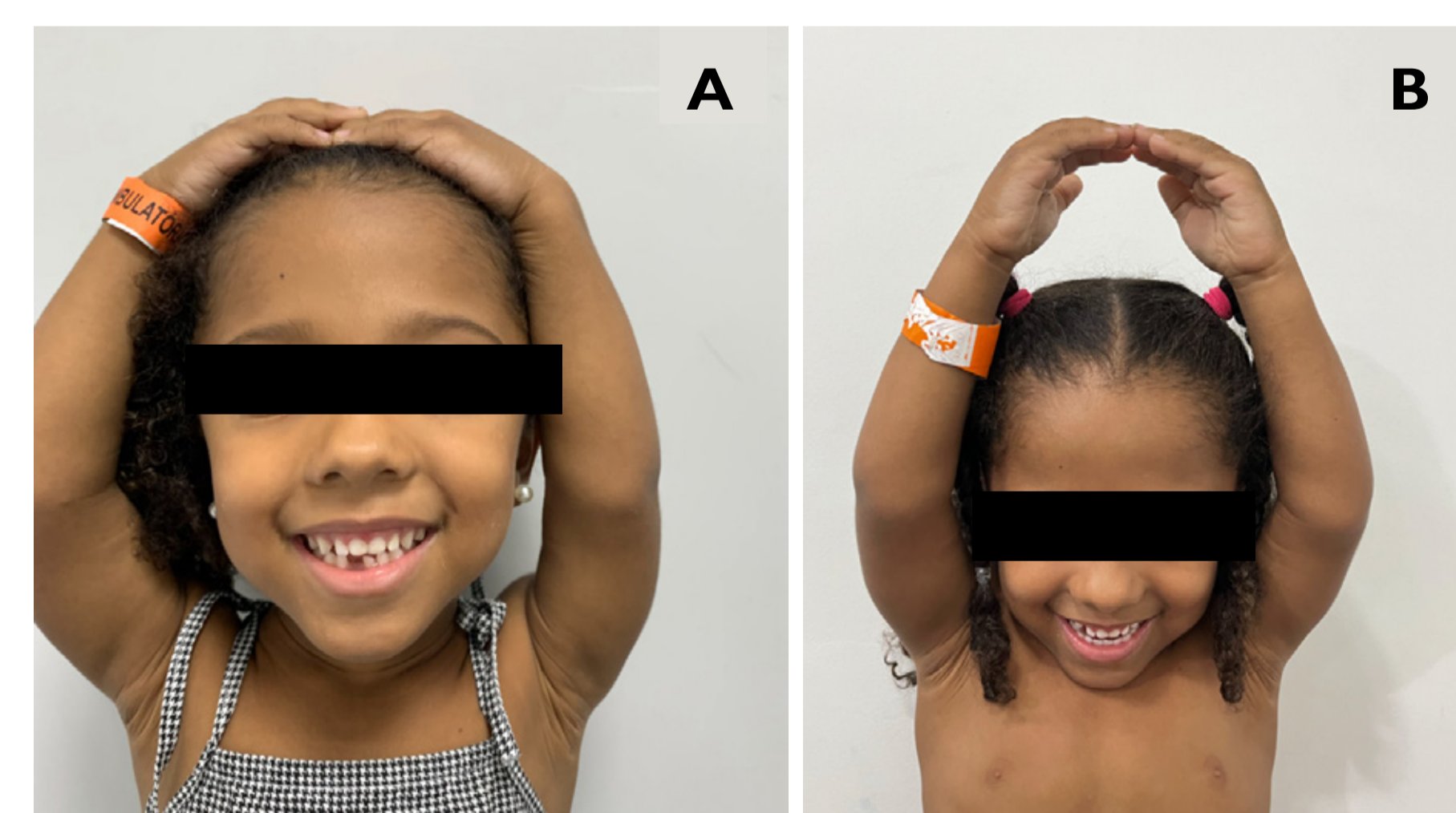
Treatment with vosoritide was well tolerated and significantly increased height velocity and height velocity SDS in patients with achondroplasia after 6 months of treatment.



**Figure 1.** Mean  $\pm$  standard deviation of height velocity (cm/year), height velocity SDS, and height SDS before and after 6 months of treatment with vosoritide (n=12).



**Figure 2.**  $\Delta$  height SDS ( $-0.74$  to  $+1.62$ ),  $\Delta$  height velocity ( $-0.98$  to  $+4.09$ ), and  $\Delta$  height velocity SDS ( $-1.23$  to  $+5.63$ ). n=12.



**Figure 3.** (A) Before treatment; (B) After 6 months of treatment with vosoritide.



**Figure 4.** Two patients (I and II) with hypertrichosis.



## ARTICLE

# Lifetime Impact Study for Achondroplasia (LISA): Findings from an observational and multinational study focused on health-related quality of life in individuals with achondroplasia in Latin America



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### ABSTRACT

**Purpose:** The multisystem clinical manifestations and complications of achondroplasia, the most common form of disproportionate short stature, can cause functional impairment and psychosocial burden. The Lifetime Impact Study for Achondroplasia (LISA), aimed to assess health-related quality of life and medical resource utilization among Latin America patients with achondroplasia.

**Methods:** Data were collected from individuals aged 3 years and above in Argentina, Brazil, and Colombia between 2018 and 2021. A total of 172 patients participated in the study.

**Results:** Children with achondroplasia reported lower scores compared with average stature children in Quality of Life in Short Stature Youth (QoLISSY) and Pediatric Quality of Life Inventory (PedsQL) questionnaires, with the greatest impact on physical and social domains. Among adolescents, a significant percentage reported pain, 10.3% experienced pain in 3 or more sites. Adults scored lower than the reference population in the EQ-5D-5L Visual Analog Score, and a considerable portion reported moderate to severe anxiety/depression, pain or discomfort, and mobility problems. The Nottingham Health Profile (NHP) revealed poor health status in terms of energy, pain, and mobility. Medical events, particularly musculoskeletal and connective tissue disorders were reported, resulting in high medical resource utilization.

**Conclusion:** Overall, the Lifetime Impact Study for Achondroplasia study provides extensive data on health-related quality of life, psychosocial impact, and health care resource utilization among individuals with achondroplasia in Latin America. The findings confirm a significant burden of illness across multiple domains for these individuals.

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## Introduction

Achondroplasia is an autosomal dominant genetic disorder caused by pathogenic variants in fibroblast growth factor receptor 3 (*FGFR3*; HGNC: 3690) gene.<sup>1,2</sup> This skeletal dysplasia is the most common form of disproportionate short stature.<sup>1</sup> Worldwide, the disease occurs approximately in 1 in 25,000 live births<sup>3</sup> and the prevalence in Latin America (LATAM) is 2.5 to 4.6 per 100,000 individuals.<sup>3,4</sup>

Achondroplasia is associated with impaired development of the bones and cartilage.<sup>3</sup> Patients typically present with disproportionate short stature, rhizomelic limb shortening, tibial bowing, narrow chest, macrocephaly with prominent forehead, midface hypoplasia, and a depressed nasal bridge.<sup>5,6</sup> Achondroplasia-related complications and comorbidities vary at different life stages.<sup>7-9</sup> More prevalent complications related to skeletal manifestations are genu varum and thoracolumbar kyphosis, occurring in infancy and childhood.<sup>7-9</sup> In infants, there is also a high prevalence of neurological and ear, nose, and throat (ENT) symptoms including spinal stenosis or compression, foramen magnum stenosis, hypotonia, and sleep-disordered breathing.<sup>7-9</sup> The neurological manifestations in the arms, neck, and legs continue in adolescence.<sup>7-9</sup> Pain is reported in all age groups, and cardiovascular conditions and obesity are more common in adulthood.<sup>7-9</sup>

Because of the multisystem and lifelong effects of achondroplasia-related symptoms and comorbidities, international and LATAM guidelines recommend a multidisciplinary approach for patient management, which includes medical, functional and psychosocial care throughout life.<sup>10,11</sup> As consequences of the clinical manifestations of achondroplasia, the developmental milestones of children living with the disease differ from average stature individuals.<sup>8</sup> The short stature, shortened limbs, ligamentous laxity, and communication issues caused by hearing and speech limitations impair or delay early developmental milestones and independence from parents or caregivers, which, in turn, can result in reduced functionality, limitations in the ability to perform daily activities, poor self-esteem, and reduced quality of life (QoL).<sup>12-14</sup> Previous studies have reported limited functionality as the main generators of child/adolescent and parental anxiety and stress according to patients and their caregivers in the United States and Spain.<sup>15,16</sup>

Although there is a consensus that achondroplasia greatly affects patients' physical functioning and psychosocial life, data related to psychosocial status of the adult achondroplasia population provide inconsistent findings. A recently published study with European patients of a broad range of ages, including adults, demonstrated that achondroplasia associates with impaired QoL and functionality, particularly related to physical domains.<sup>17</sup> Some reports even show, by using patient-reported health-related QoL (HRQoL) surveys, that patients' mental scores are similar to standard values found in general population, meanwhile the physical component score is significantly reduced.<sup>18-20</sup> However, in these studies, the higher-than-expected scores in the physical and mental

components are not necessarily representative of the general achondroplasia population. The higher than expected mental component scores can be explained by the fact that the majority of the participants in both of the studies belonged to, and were supported by, patient's associations that contributed to healthier mental function, whereas the decline in physical scores is usually associated with musculoskeletal complaints in elderly population, a cohort found in a reduced number in these studies.<sup>18,19</sup> Data from other studies, such as that by Jennings et al and Gollust et al, describe reduced QoL and significant levels of depression and anxiety in adults with achondroplasia, which was correlated with chronic pain.<sup>12,20</sup>

Although there are a number of studies on the natural history of achondroplasia and its psychosocial burden, to date, there is a lack of published data on the lifetime burden associated with living with the condition, especially in the LATAM population. Of note, a recently published systematic literature review evidenced the high burden of achondroplasia on affected individuals and on health care resources in LATAM countries.<sup>4</sup> However, the interpretation and comparison of outcomes was confounded/limited by the heterogeneity of the clinical and methodological characteristics of the studies, mainly because of small sample sizes.

The Lifetime Impact Study for Achondroplasia (LISA; NCT03872531) was an observational study that aimed to describe and quantify the lifetime impact of achondroplasia in affected individuals in LATAM. Here, we report the findings from LISA, describing the clinical and psychosocial burden, HRQoL, and health care resource use of a LATAM population of patients with achondroplasia.

## Materials and Methods

### Study design

The LISA (NCT03872531) was a multinational, observational, retrospective study with a cross-sectional component assessing HRQoL among individuals living with achondroplasia in LATAM.

The study took place in 4 sites across 3 LATAM countries, Argentina, Brazil, and Colombia. All the sites provide multidisciplinary consultancy for patients with achondroplasia.

### Sample population

Table 1 shows the main characteristics of the LISA study population. The study enrollment occurred from 2 January 2018 to 16 July 2021. Enrollment into the study was divided by age groups as detailed in Table 1. The number of participants included who had limb lengthening surgery was limited to 20% to minimize selection bias.

The inclusion criteria for the study were as follows:  $\geq 3$  years of age at time of enrollment, have a documented diagnosis of achondroplasia based on genetic or clinical/

**Table 1** LISA participants by age, country, and/or analysis subgroups

LISA Participants	<i>n</i> (%)
Number of recruited patients per age group (years)	175 (100)
3-5	20 (11.4)
6-10	30 (17.1)
11-15	30 (17.1)
16-20	20 (11.4)
21-30	20 (11.4)
31-40	20 (11.4)
≥41	35 (20.0)
Number of enrolled patients	172 (100)
Argentina	37 (21.5)
Brazil	94 (43.0)
Colombia	41 (23.8)
Discontinuations	0 (0)
Study analysis sets	
Enrolled Analysis Set (EAS) <sup>a</sup>	172 (100)
Pediatric History Analysis Set (PHAS) <sup>b</sup>	32 (18.2)
Historical data (PHAS) <sup>c</sup> by age (years)	32 (100)
3	4 (12.5)
4	5 (15.6)
5	5 (15.6)
6	2 (6.3)
7	4 (12.5)
8	0 (0.0)
9	2 (6.3)
10	0 (0)
>10	10 (31.3)

EAS, Enrolled Analysis Set; PHAS, Pediatric History Analysis Set.

<sup>a</sup>EAS, Enrolled Analysis Set—all enrolled patients.

<sup>b</sup>PHAS, Pediatric History Analysis Set—patients with at least a 3-year complete medical history before 18 years of age.

<sup>c</sup>The earliest date of medical history entered into the study database before enrollment.

radiological findings, cognitive and linguistic capacities necessary to complete questionnaires in the language of his/her country (and/or parents/legal representatives, as applicable), and have medical records available for at least the 3 years before the date of enrollment. The exclusion criteria were as follows: current or prior participation (in the previous 6 months) in any clinical trial of a medicinal product or medical device or in any BioMarin study. It should be noted that not all patients had genetic confirmation because this was not a requisite inclusion criterion.

### Data collection, management, and statistical analysis

Data about QoL, psychosocial and socioeconomic factors, and health care resource use were collected using questionnaires validated for local use. An electronic data capture (EDC) system (Classic Rave EDC 2020.2.0) was developed to receive the data collected in this study, including data entry screens and automated edit and logic checks to

validate test data. The data collected from medical records and questionnaires were entered into the EDC system by trained study staff or a designee.

For data analysis, the population was divided into 2 sets, as displayed in [Table 1](#): the Enrolled Analysis Set (EAS, *n* = 172), which included all enrolled participants who had consented to participate and met the inclusion criteria and was used for the study disposition, protocol deviations, demographic, and medical history summaries and analysis; and the Pediatric History Analysis Set (PHAS, *n* = 32), which included all participants with at least a 3-year complete medical history (meaning that all, or the vast majority, of medical records were available for the period) before 18 years of age. The PHAS population was used to analyze events related to medical history, health care resource use, and concomitant medication. The PHAS population were all from Argentina because this site had access to a comprehensive set of medical records.

The analyzed data were stratified by patient age (3-5, 6-10, 11-15, 16-20, 21-30, 31-40, and ≥41 years). Statistical analysis was carried out using SAS Institute Inc 2013 SAS/ACCESS 9.4 Interface to Adaptable Database System. The continuous variables were described by their mean, standard deviation, median, quartiles 1 and 3, extreme values (minimum and maximum), and the number of missing data items. Categorical variables were described (counts) by the absolute and relative (%) frequency of each class and the number of missing data items.

### Patient- and parent-reported outcomes questionnaires

At the time at enrollment, health-related questionnaires were completed related to the self-perceived impact of achondroplasia in daily life by the participants, or by their parents/caregivers/legal representatives in the case of minors. The questionnaires were divided into child/adolescent—Pediatric Quality of Life Inventory Questionnaire (PedsQL), Quality of Life in Short Stature Youth (QoLISSY), Pediatric Functional Independence Measure (WeeFIM), Adolescent Pediatric Pain Tool (APPT), and adult—5-level EQ-5D version of EuroQoL (EQ-5D-5L), Nottingham Health Profile (NHP), Brief Pain Inventory - Short Form (BPI-SF), and Work Productivity and Activity Impairment (WPAI). The outcome domains assessed in each one is shown in [Supplemental Table 1](#). The questionnaires were given to the participants during a routine hospital visit or sent to his/her home, with the exception of the WeeFIM, which was applied by an investigator during a hospital visit or at a mutually convenient time over the telephone.

The scores obtained were compared with values found for the reference population, average stature individuals, or participants with other conditions affecting height, when available.

**Table 2** Demographic characteristics at time of enrollment of patients with achondroplasia

Demographic Characteristics	Enrolled Analysis Set (EAS) <sup>a</sup>				Pediatric History Analysis Set (PHAS) <sup>b</sup>
	Brazil	Argentina	Colombia	Overall	Argentina
Participants per country, <i>n</i> (%)	94 (54.6)	37 (21.5)	41 (23.8)	172 (100.0)	32 (100.0)
Gender, <i>n</i> (%)					
Male	45 (47.9)	19 (51.4)	17 (41.5)	81 (47.1)	18 (56.3)
Female	49 (52.1)	18 (48.6)	24 (58.5)	91 (52.9)	14 (43.8)
Age (years)					
Median (25th, 75th Percentile)	18.5 (9.0, 32.0)	15.0 (7.0, 23.0)	16.0 (10.0, 32.0)	16.0 (8.0, 31.5)	12 (6.5, 17.5)
Min, Max	3, 65	3, 50	3, 71	3, 71	3, 43
Age subgroups (years) <sup>c</sup> , <i>n</i> (%)					
3-5	11 (11.7)	5 (13.5)	4 (9.8)	20 (11.6)	5 (15.6)
6-10	18 (19.1)	9 (24.3)	8 (19.5)	35 (20.3)	9 (28.1)
11-15	16 (17.0)	6 (16.2)	7 (17.1)	29 (16.9)	6 (18.8)
16-20	5 (5.3)	6 (16.2)	5 (12.2)	16 (9.3)	6 (18.8)
21-30	15 (16.0)	5 (13.5)	5 (12.2)	25 (14.5)	4 (12.5)
31-40	17 (18.1)	1 (2.7)	5 (12.2)	23 (13.4)	1 (3.1)
41 or more	12 (12.8)	5 (13.5)	7 (17.1)	24 (14.0)	1 (3.1)
Limb lengthening before enrollment <sup>d</sup> , <i>n</i> (%)					
Yes	2 (2.1)	3 (8.1)	7 (17.1)	12 (7.0)	3 (9.4)
Time since limb lengthening (years) <sup>e</sup>					
Median (25th, 75th Percentile)	5.2 (1.9, 8.5)	11.6 (2.8, 29.2)	6.0 (2.3, 8.7)	6.4 (2.6, 10.2)	11.6 (2.8, 29.2)
Min, Max	2, 9	3, 29	1, 18	1, 29	3, 29

EAS, Enrolled Analysis Set; PHAS, Pediatric History Analysis Set.

<sup>a</sup>All enrolled patients.

<sup>b</sup>Patients with at least a 3-year complete medical history before 18 years of age.

<sup>c</sup>When date of birth is missing or only the year is provided, age collected by the electronic case report form (eCRF) is used.

<sup>d</sup>Assessment closest to enrollment date.

<sup>e</sup>Time (years) since limb lengthening surgery (date of enrollment, earliest date of limb lengthening surgery)/365.25.

## Results

### Demographic and baseline characteristics of the patients with achondroplasia

The study enrolled a total of 172 participants: 37 in Argentina (1 site), 94 in Brazil (2 sites), and 41 in Colombia (1 site) (Tables 1 and 2). All enrolled participants met the inclusion criteria and completed the study. The demographic and baseline characteristics at the time of enrollment are described in Table 2. The age subgroups and gender distribution were homogenous, as predicted by the study design, with 81 (47.1%) males and 91 (52.9%) females with a median age across both genders of 16.0 years (Table 2). Similar to the EAS, the Argentinean PHAS population had a relatively equal gender distribution, 18 (56.3%) males and 14 (43.8%) females (Table 2). However, as only pediatric data were included, as expected, the median age was younger (12.0 years old). For the 8 (25%) participants aged  $\geq 18$  years at baseline from the PHAS, only data from their pediatric medical history were used in the analysis.

In total, 12 (7%) individuals from EAS underwent limb lengthening before enrollment, with a median time since surgery of 6.4 years (Table 2). Notably, in Colombia, a greater proportion of individuals had undergone a limb lengthening procedure ( $n = 7$  of 41, 17.1%), compared with

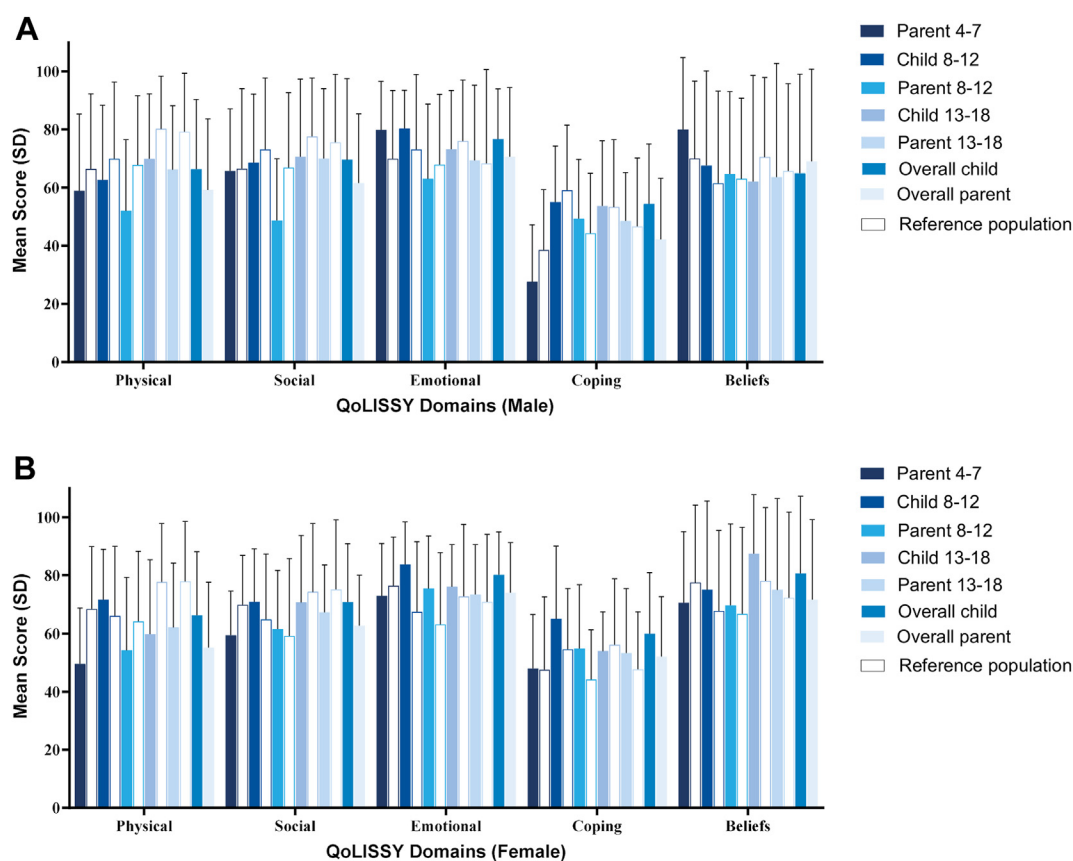
3 of 37 participants (8.1%) in Argentina and 2 of 94 participants (2.1%) in Brazil. In the PHAS population, only a single male pediatric and 2 female adult participants had undergone limb lengthening.

In the EAS population, achondroplasia diagnosis was generally made very early in life, with a median age at diagnosis of 0.7 months. Some participants were diagnosed much later in life, with 1 participant in Brazil being diagnosed at 46.9 years. This variability in time to diagnosis is reflected by the mean (SD) age at diagnosis of 26.4 (80.85) months. Diagnostic practice differed between countries, with patients in Argentina being much more likely to have their diagnosis confirmed by genetic testing (75.7% of participants, compared with 40.4% in Brazil and 17.1% in Colombia). Genetic testing was not used as the initial method of diagnosis in Argentina and only very occasionally in Brazil and Colombia. Among the individuals with a genetic test, the most common *FGFR3* gene pathogenic heterozygous variants were c.1138G>A ( $n = 61$ , 91.0%) and c.1138G>C ( $n = 3$ , 4.5%), which was consistent across the 3 countries.

### Patient- and parent-reported outcomes

#### Children and adolescent QoL and psychosocial burden

The QoLISSY questionnaire evaluated child- and/or parent-perceived scores related to physical, social, emotional,



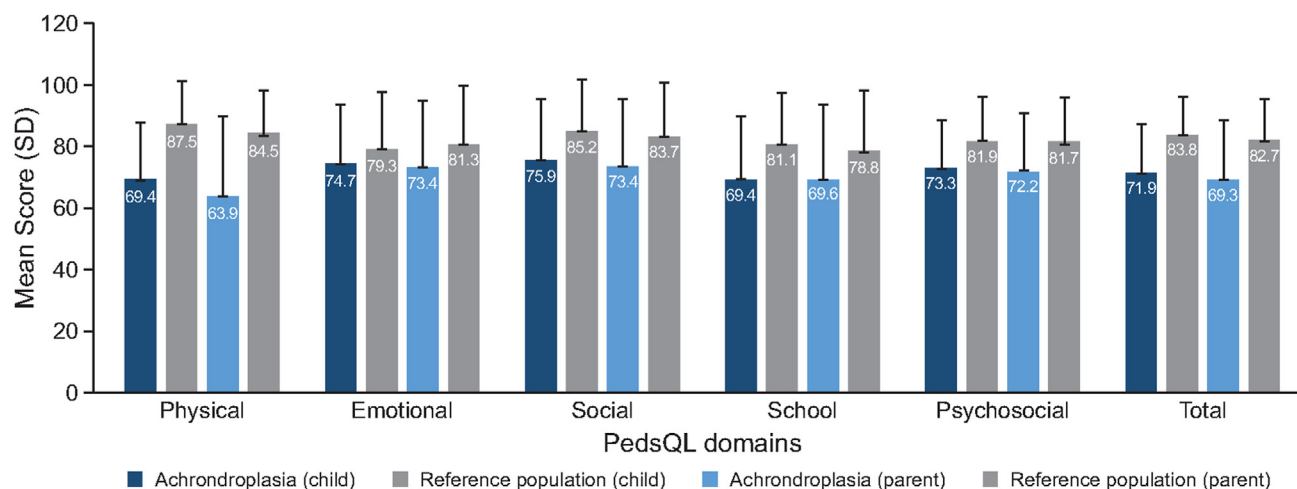
**Figure 1** Quality of Life in Short Stature Youth (QoLISSY) scores for male and female child/adolescent achondroplasia participants. Child- and parent-perceived mean scores related to physical, social, emotional, coping, and beliefs domains for male (A) and female (B) patients with achondroplasia in comparison to the reference population (empty bars; average stature children). The QoLISSY scores ranged from 0 (poor quality of life) to 100 (better quality of life) and are presented as the mean score and its standard deviation (SD). QoLISSY, Quality of Life in Short Stature Youth.

coping, and beliefs domains, with a possible score of 0 (poor QoL) to 100 (better QoL). A total of 87 (96.6%) of 90 participants completed the QoLISSY questionnaire. The total QoLISSY score for questionnaires completed by patients (mean [SD] = 71.5 [17.5]) were higher than that for parent proxies (mean [SD] = 63.8 [18.9]), and the scores for patients and parents were lower than that for the reference population of average stature children (83.8 [12.7] and 82.7 [12.7], respectively). For the individual domains, patients with achondroplasia scored lowest in physical and social domains (Figure 1). In general, there were only small variations in the scores across age groups (Figure 1). In comparison with the average stature children, the scores of patients with achondroplasia are comparable or slightly lower in most domains (the largest score difference was 10 points), regardless of the gender or age range (Figure 1).

A second questionnaire was used to evaluate HRQoL and psychosocial burden in the achondroplasia child/adolescent population, the PedsQL, which rates child- and parent-perceived physical, emotional, social, school, and psychosocial functioning. Individual domains and total score values for the child version of the questionnaire were similar across Argentina, Brazil, and Colombia (Supplemental Figure 1). The total PedsQL score was slightly lower

according to parents' reports compared with the child version, with mean values of 71.9 for children and 69.3 for parents (Figure 2). Parents- and child-perceived scores for the individual domains were similar and all domains scored lower than the reference population (average stature children), particularly for the physical domain (Figure 2). The highest scores in the PedsQL for the patients with achondroplasia were in the emotional and social domains (Figure 2).

The functional skills and performance in daily activities in the children from 5 to 17 years old were measured using the WeeFIM instrument.<sup>21,22</sup> WeeFIM is a questionnaire with 18 items that cover self-care, mobility, and cognition domains and assesses the need for assistance and the severity of disability, with higher scores indicating greater independence.<sup>21,22</sup> The individual scores of the 3 evaluated domains, as well as the overall mean total scores, were similar across Argentina, Brazil, and Colombia (Supplemental Figure 2). The overall WeeFIM score increased with age, suggesting that older children (aged 13-17 years old) are more independent in terms of self-care, mobility, and cognition (Table 3). Despite the small number of patients that had the limb lengthening surgery, scores were higher for this group when compared with the overall



**Figure 2 Pediatric Quality of Life Inventory (PedsQL) for the child/adolescent achondroplasia participants.** Child- and parent-perceived scores (represented in dark and light blue bars, respectively) related to physical, emotional, social, school, and psychosocial functioning domains, as well as the total score compared with the reference population (gray bars, average stature children or proxy reference population [parent]). Scores on the PedsQL domains range from 0 (poor HRQoL) to 100 (better HRQoL). Data are presented as the mean score and its standard deviation (SD). PedsQL, Pediatric Quality of Life Inventory.

achondroplasia children (Table 3), especially for 2 participants who had undergone upper limb (humerus) surgery and reported the highest self-care scores.

#### Adult QoL, psychosocial, and socioeconomic burden

The HRQoL and psychosocial and socioeconomic burden because of achondroplasia was assessed in adults from the EAS population.

These parameters were initially evaluated through the EuroQoL (EQ-5D-5L) questionnaire, an instrument that measures health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression dimensions, through a visual analog scale (VAS, measuring overall self-rated health status and ranging from 0, the worst health, to 100, the best health) and the Utility Index Score (UIS, assesses overall health status and ranges from -0.6, poorest health, to 1.0, better health). All adults completed the EQ-5D-5L. Of the 79 adult participants, 16 (20.3%) had moderate to severe problems with mobility (walking), 10 (12.7%) with self-care (washing or dressing themselves), and 14 (17.8%) with doing their usual activities (Figure 3A-C, respectively). Moreover, 21 (26.6%) reported moderate or severe anxiety/depression, and 20 (25.3%) reported moderate to severe pain or discomfort (Figure 3D and E, respectively). Despite these results, the mean (SD) EQ-5D-5L VAS score was lower than the unaffected population, 72.7 (20.1) versus 80.1 (25.3); and the UIS values of the achondroplasia and reference populations were comparable, 0.9 (1.4) versus 0.9 (0.2) (Supplemental Figure 3). The mean VAS score was lowest in Brazil (mean, SD of 68.3, 18.1) and highest in Colombia (mean, SD of 83.6, 20.5) (Supplemental Figure 3), reflecting the higher rates of anxiety and depression reported in Brazil (Figure 3C), whereas the UIS values were similar across countries (Supplemental Figure 3). Although 5 adult participants had

undergone limb lengthening surgery, the overall mean VAS score (72.7) was similar to the non-limb-lengthened population.

The NHP was used to assess energy, pain, emotional reactions, sleep, social isolation, and physical mobility. Individual and total scores range from 0 (good subjective health status) to 100 (poor subjective health status). Seventy-seven (97.5%) adults completed the NHP. The mean total score was 25.8 (SD 21.59) and was similar among the countries, ranging from a mean of 25.1 (19.81) in Brazil to 27.0 (24.36) in Colombia. The highest scores, that indicate poor health status, were for energy, pain, and mobility, with respondents stating that they found it hard to stand for long ( $n = 47$ , 59.5%), hard to reach for things ( $n = 46$ , 58.2%), lost energy quickly ( $n = 45$ , 57.0%), were unable to wake up early ( $n = 38$ , 48.1%), had pain when walking ( $n = 37$ , 46.8%), had trouble getting up and down the stairs ( $n = 36$ , 45.6%), and found it hard to get dressed by themselves ( $n = 17$ , 21.5%). Five adults who had undergone limb lengthening surgery scored higher than the general adult population, with a mean (SD) of 40.6 (24.17), indicating poor subjective health, especially in the energy and social isolation domains. The individuals scores for general adult and limb-lengthened population are detailed in Table 4.

The WPAI questionnaire was used to investigate the extent to which achondroplasia affects employment, work productivity, the ability to work, and the ability to perform regular daily activities other than work. All the 79 adult participants completed the questionnaire and 47 (59.5%) reported being employed. The percentages of employment varied widely between countries, with Argentina reporting only 1 (7.7%) patient as employed against 36 (76.6%) Brazilian adults employed. The mean number of hours worked was 27.4 (SD 16.94), and the perceived impact of

**Table 3** Pediatric Functional Independence Measure (WeeFIM) scores for overall achondroplasia child/adolescent population and patients who underwent limb lengthening surgery by age group

WeeFIM Domain Scores	Children/Adolescent; Mean (SD)				Children/Adolescent With Limb Lengthening Surgery; Mean (SD)			
	Age: 5-17 (n = 89)	Age: 5-7 (n = 22)	Age: 8-12 (n = 31)	Age: 13-17 (n = 27)	Age: 5-17 (n = 7)	Age: 5-7 (n = 0)	Age: 8-12 (n = 3)	Age: 13-17 (n = 4)
Self-care <sup>a</sup>	32.1 (5.73)	37.4 (8.36)	49.8 (6.84)	54.6 (2.94)	53.8 (5.31)	-	51.7 (7.51)	56.0 (0.00)
Mobility <sup>b</sup>	31.6 (6.52)	28.4 (5.64)	33.6 (2.55)	34.7 (0.74)	35.0 (0.00)	-	35.0 (0.00)	35.0 (0.00)
Cognition <sup>b</sup>	32.1 (5.73)	30.1 (6.78)	33.8 (2.94)	34.8 (0.61)	33.7 (3.27)	-	32.3 (4.62)	35.0 (0.00)
Motor <sup>b</sup>	76.8 (16.79)	65.8 (10.36)	83.5 (8.51)	89.3 (3.46)	88.8 (5.31)	-	86.7 (7.51)	91.0 (0.00)
Overall score <sup>c</sup>	109.9 (20.74)	95.9 (15.34)	117.2 (9.19)	124.1 (3.51)	122.5 (8.57)	-	119.0 (12.12)	126.0 (0.00)

WeeFIM, Pediatric Functional Independence Measure.

<sup>a</sup>Range from 8 to 56.

<sup>b</sup>Range from 5 to 40.

<sup>c</sup>Range from 18 to 126. Lower scores indicate "Total assistance" and higher scores "Complete independence."

achondroplasia on work productivity was 1.3 (2.40) on a scale from 0 (no effect) to 10 (high effect). Although the patients reported having little time off work because of achondroplasia (1.4% of work time missed), a greater proportion of participants reported being impaired at work (13.8%) or during regular daily activities (23.1%).

### Pain in children/adolescent, adult, and overall achondroplasia population

In order to investigate the impact of pain and discomfort in patients with achondroplasia, 2 pain-related questionnaires, the APPT (for adolescent participants aged 8 to 17 years) and the Brief Pain Inventory (BPI, for adult participants with 18 years old or more) were utilized.

Fifty-seven (98.3%) adolescents and all adult participants completed the pain questionnaires. Among the adolescents, 53.4% reported at least 1 pain site, and 10.3% reported 3 or more pain sites. For the adult population, 58 (73.4%) reported experiencing pain not described as everyday minor aches and pain. The most common locations of pain reported by the adolescents and adults are detailed in Figure 4. Pain in the right and left knees and left shoulder were the main complaints of the adolescents, whereas adults reported pain in the head, lower spine, and right shoulder (Figure 4). Similar results were observed in all countries for both child/adolescent and adult populations, except for the APPT temporal score, which was higher in Argentina, and scores for the BPI, which were lower in Colombia (Supplemental Figure 4).

### Burden of medical complications in pediatric population with achondroplasia

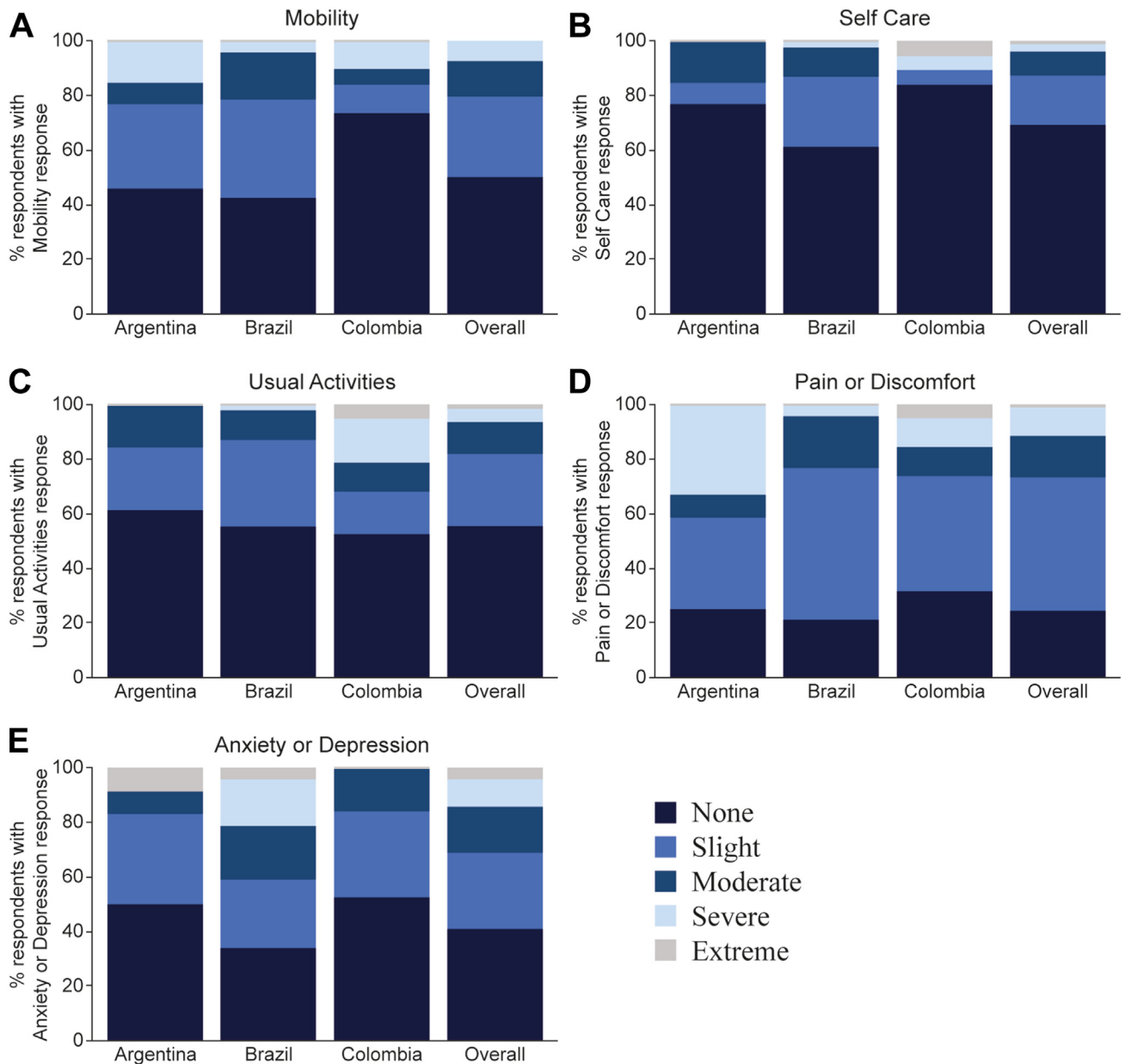
Data from Argentinean achondroplasia pediatric population ( $n = 32$  participants, the PHAS population) was analyzed separately. Almost all participants ( $n = 31$ , 96.9%) in this population had a history of achondroplasia-related medical events, with 130 events reported in 30 participants. The most common reported events by organ system classes

reported ( $\geq 20\%$ ) were musculoskeletal and connective tissue disorders (accounting for 78.1% of the events), ear and labyrinth disorders (59.4%), infections (53.1%), thoracic disorders (50.0%), and nervous system disorders (46.9%). The events reported by their rate are shown in Figure 5. Except for knee deformity (the most commonly reported medical event, reported by 20 participants with an event rate of 7.02 per 100 person-years), the highest event rates were in the youngest age range ( $<3$  years), with decreasing incidences observed in the older age groups (3-10 and 11-17 years) (Figure 5).

The majority of the pediatric participants, 28 (87.5%), reported a history of use of at least 1 medication, defined as any medications taken in the participants' entire medical history. In line with the most reported medical events being related to musculoskeletal and connective tissue disorders (Figure 5), which were also reported as the main cause of pain (Figure 4), analgesics were the most prescribed class of medication—19 individuals (59.4%, event rate of 12.64) reported the use of this type of medication, followed by antibacterials for systemic use ( $n = 17$ , 53.1%, event rate 9.83), anti-inflammatories and antirheumatics ( $n = 17$ , 53.1%, event rate 9.48), corticosteroids for systemic use ( $n = 5$ , 15.6%, event rate 2.46), and drugs for obstructive airway diseases ( $n = 4$ , 12.5%, event rate 2.81). This pattern was consistent among the 3 age groups of the PHAS population ( $<3$ , 3-10 and 11-17 years).

This clinical burden caused by achondroplasia also led to high rates of medical resource use, which included medical examinations, health care professional (HCP) and in/outpatient hospital visits, and surgical procedures. Ten participants (31.3% of the PHAS population) reported 35 medical examinations in their medical history (Table 5). The age range with the most medical examinations was 3-10 years old (7 participants, 23.3%, event rate of 15.40) and an audiogram was the most common medical examination (Table 5), which correlates with the high rates of ear disorders reported among this population (Figure 5).

All 32 patients in the PHAS population reported at least 1 HCP visit, with a total of 2177 events over 285 person-years



**Figure 3** Individual dimensions of the EuroQoL (EQ-5D-5L) in adult achondroplasia participants. Percentage of adults reporting different levels (from none to extreme, according to the colored legend) of mobility (A), self-care (B), usual activities performance issues (C), feeling of pain or discomfort (D), and anxiety or depression (E) by country and the overall population.

of medical history. The list of the type of HCP visited is detailed in Table 5. Disease follow-up was the main reason for HCP visits (reported by 12 participants, overall event rate of 5.62), and a physiotherapist was the most visited HCP in all

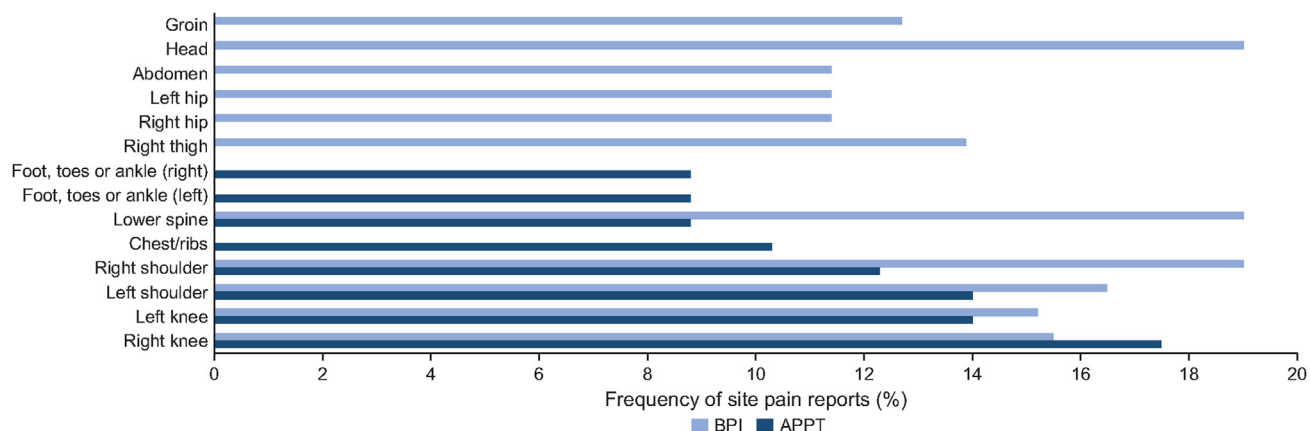
age groups (<3, 3-10 and 11-17 years), being more common in the <3- and 11-17-year age groups (Table 5).

Moreover, 71.9% of participants reported an inpatient visit, with 53 events occurring in 23 patients (event rate

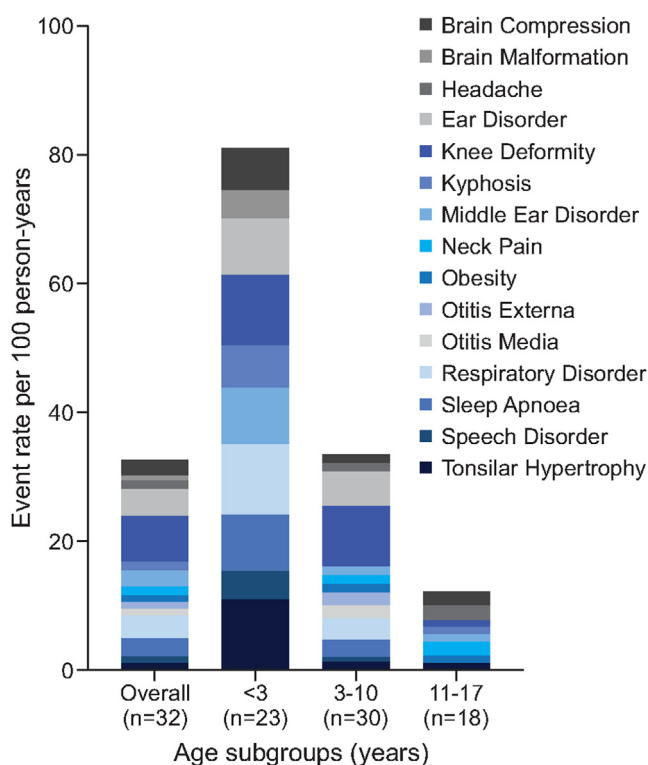
**Table 4** Nottingham Health Profile (NHP) of achondroplasia adult population and patients who underwent limb lengthening surgery

Achondroplasia Patients	Mean (SD) Scores for NHP Individual Domains <sup>a</sup>					
	Energy	Pain	Emotion	Sleep	Social Isolation	Physical Mobility
Adults ( <i>n</i> = 79)	35.4 (36.54)	29.3 (29.61)	22.5 (22.95)	25.6 (29.98)	12.8 (21.50)	29.3 (26.30)
Limb lengthening surgery ( <i>n</i> = 5)	64.8 (48.94)	39.3 (39.44)	33.8 (6.16)	30.3 (32.15)	34.7 (11.59)	41.0 (34.93)

<sup>a</sup>Individual and total scores range from 0 (good subjective health status) to 100 (poor subjective health status).



**Figure 4** Most common pain locations reported in the Adolescent Pediatric Pain Tool (APPT) and adult Brief Pain Inventory (BPI) questionnaires. Most frequent pain site locations reported in the APPT (dark blue bars) and BPI (light blue bars) questionnaires by child/adolescent and adult populations. APPT, Adolescent Pediatric Pain Tool; BPI, Brief Pain Inventory.



**Figure 5** Achondroplasia-related medical events by age group in the PHAS population. Data are presented as event rates per 100 person-years, calculated as the total number of events divided by the total number of patient historical years multiplied by 100. Patients were included in the age groups according to the age at which the medical event was reported. Because each patient could have presented several events across their pediatric lifespan, they may be included in multiple age groups. Data related to ear disorders were collected from medical records during the COVID-19 pandemic, thus hampering onsite data gathering and harmonization by study monitors. To preserve information as they are classified in each site, we presented information separately and classified them in accordance with the MedRA categories (version 22.0).

18.60). “Other ENT issues” are listed as the most common reason for inpatient hospital visits, with an event rate of 9.83 in 13 participants, occurring mainly in the 3-10 age range (Table 5 and Figure 6A). “Other” (including adenotonsillectomy, sleep studies, gastrointestinal disorders, and ventriculoperitoneal shunt surgery) was the second most reported event, with an event rate of 2.81 ( $n = 6$  participants), followed by genu varum/valgum, with an event rate of 2.46 ( $n = 6$ ) (Table 5 and Figure 6A). Twenty-eight participants (87.5%) reported outpatient hospital visits with 448 events, with higher total number of events being reported in the age ranges of 3 to 10 (205) and 11 to 17 (189) years (Table 5 and Figure 6B). Pediatricians (150 events in 27 participants) and orthopedists (89 events in 22 participants) were the specialists most visited during outpatient visits (Table 5 and Figure 6B).

Twenty-four (75%) participants reported a surgery with 54 events across the 285 person-years of medical history, the highest incidence being in the 3 to 10 age group (Figure 6C). The event rate of surgical procedures increases with the age groups and the highest was found in the 11-to-17-year age group ( $n = 11$  participants, event rate 22.26) (Figure 6C). As expected for achondroplasia patients, younger children (<3 years) most commonly underwent adenotonsillectomy (event rate 6.57, with 3 participants reporting it over a relatively short time period) and spinal decompression procedures (Figure 6C). From age 3 to 10 years, the most common surgeries were adenotonsillectomy and myringotomy (tied for the highest event rate of 2.68, reported by 4 participants each), and surgeries related to limbs and osteotomy were also reported. In the 11-to-17-year age group, the highest event rate was for osteotomy at 5.56, reported by 4 participants. The 3 patients who underwent limb lengthening surgery reported at least 1 surgical event, with a total of 12 events reported. All of them underwent osteotomy surgery.

**Table 5** Medical resource use of achondroplasia pediatric patients

Types of Medical Resource Use	Number of Events (Event Rate) <sup>a</sup> by Age Group <sup>b</sup>			
	< 3 Years (n = 23)	3-10 Years (n = 30)	11-17 Years (n = 18)	Overall (n = 32)
Patient historical years <sup>c</sup>	45.69	149.38	89.85	284.91
Medical examination				
Total number of events (event rate per 100 person-years)	2 (4.38)	23 (23.3)	10 (11.13)	35 (12.28)
Audiogram	0	2 (1.34)	1 (1.11)	3 (1.05)
Biopsy	0	0	1 (1.11)	1 (0.35)
Brain stem auditory evoked response	0	0	1 (1.11)	1 (0.35)
Computerized tomogram head	0	2 (1.34)	0	2 (0.70)
Computerized tomogram spine	0	3 (2.01)	0	3 (1.05)
Health care professional visit				
Total number of visit events (event rate per 100 person-years)	9 (19.70)	9 (6.03)	5 (5.56)	23 (8.07)
ENT physician and/or surgeon	0	1 (0.67)	0	1 (0.35)
Occupational Therapist	0	1 (0.67)	0	1 (0.35)
Orthotist	0	1 (0.67)	0	1 (0.35)
Pediatrician	0	1 (0.67)	1 (1.11)	2 (0.70)
Physiotherapist	7 (15.32)	1 (0.67)	4 (4.45)	12 (4.21)
Inpatient hospital visit				
Total number of visit events (event rate per 100 person-years)	10 (21.89)	24 (16.07)	18 (20.03)	53 (18.60)
Foramen magnum syndrome/stenosis	1 (2.19)	2 (1.34)	0	3 (1.05)
Genu varum/valgum	0	2 (1.34)	5 (5.56)	7 (2.46)
Limb lengthening	0	0	6 (6.68)	6 (2.11)
Other	5 (10.94)	2 (1.34)	1 (1.11)	8 (2.81)
Other ENT issues	4 (8.76)	17 (11.38)	6 (6.68)	28 (9.83)
Pain	0	1 (0.67)	0	1 (0.35)
Outpatient hospital visit <sup>d</sup>				
Total number of visit events (event rate per 100 person-years)	55 (120.38)	205 (137.24)	189 (210.36)	449 (157.59)
ENT physician and/or surgeon	6 (13.13)	30 (20.08)	22 (24.49)	58 (20.36)
Neurologist	1 (2.19)	9 (6.03)	14 (15.58)	24 (8.42)
Neurosurgeon	4 (8.76)	24 (16.07)	18 (20.03)	46 (16.15)
Orthopedist	8 (17.51)	44 (29.46)	37 (41.18)	89 (31.24)
Pediatrician	31 (67.85)	67 (44.85)	52 (57.88)	150 (52.65)

ENT, ear, nose, and throat.

<sup>a</sup>Event rates per 100 person-years were calculated as the total number of events divided by the total number of patient historical years multiplied by 100.

<sup>b</sup>Age group is based on age at time of event. Patients may be counted in multiple columns.

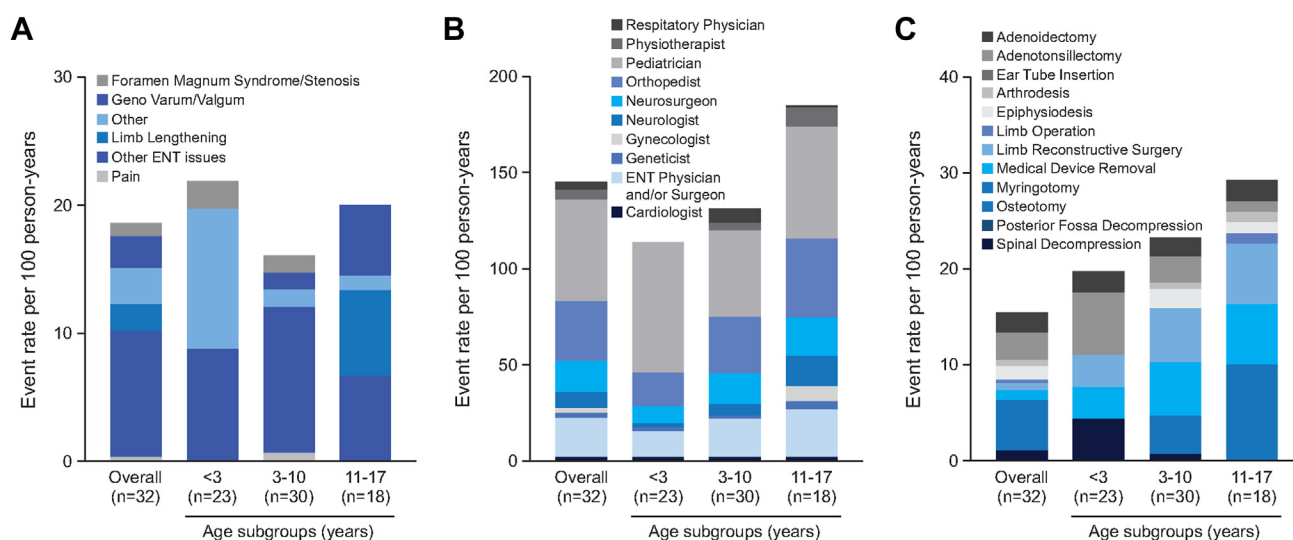
<sup>c</sup>Patient historical years are defined as the time between earliest collected history and enrollment date.

<sup>d</sup>Only the top 5 specialists (by total number of event rate) are listed.

## Discussion

LISA was the largest retrospective, observational, cross-sectional study assessing HRQoL ever undertaken that set out to characterize and quantify the lifetime impact of achondroplasia on patients in LATAM. The study was conducted at 4 sites in 3 countries, 2 sites in Brazil, 1 in Colombia, and 1 in Argentina. The COVID-19 pandemic made the recruitment of participants (particularly in Brazil) and the ability to source the complete medical record of the patients difficult. Despite this, 172 of the planned 175 participants were enrolled, and all completed the study. The sample presented a broad age range, with median age of 16.0 years, and were homogenous across the countries and the data analysis sets, with exception of the PHAS, which only comprised pediatric patients. Individuals were diagnosed early, with a median age of diagnosis of 0.7 months.

Achondroplasia-related symptoms, complications, and comorbidities greatly affect patients' physical functioning and psychosocial life, leading to a poorer QoL in some areas when compared with average stature people. Regardless of the age group and country, children and adolescents from the LISA cohort presented suboptimal HRQoL parameters, as measured by lower scores in several domains of the QoLISSY and PedsQL instruments. The overall QoLISSY scores were generally in the 60 to 70 range, indicating that HRQoL was below average compared with the reference population of average stature individuals (total QoLISSY score around 82). The lowest individual scores in the QoLISSY were in respect of the physical and social domains, which reflects the multiple challenges that patients have to face and the associated reduced accessibility and independence, reduced self-esteem, and socialization issues.<sup>13-15</sup> Parent-reported scores were generally lower than the patients' self-reported scores in the QoLISSY



**Figure 6 History of medical resource use by age group for the PHAS population.** Data of inpatient (A) or outpatient (B) hospital visits and surgical procedures (C) are presented as event rates per 100 person-years, calculated as the total number of events divided by the total number of patient historical years multiplied by 100. For the hospital visits, a patient may have more than 1 visit coded to the same category but is counted only once per category. For the surgery history, patients were included in the age group according to the age at the time of procedure and the participants may be counted in multiple groups. The medical history is reported using the MedDRA preferred terms (version 22.0). ENT, ear, nose, and throat.

questionnaire, indicating that parents perceive a more negative impact of the disease in their children QoL than the patients themselves. Other studies also demonstrated this trend.<sup>17,23</sup>

The Lifetime Impact of Achondroplasia in Europe (LIAISE), a similar study recently undertaken with European patients with achondroplasia in 6 countries (Denmark, Austria, Germany, Sweden, Spain, and Italy) also showed reduced scores across most domains of the QoLISSY and PedsQL questionnaires.<sup>17</sup> However, emotional functioning was rated high based on the QoLISSY instrument in both LISA and LIASE studies, indicating good mental/emotional-related QoL. Good emotional health was also observed for patients with other chronic medical conditions because of their improved ability to accept themselves and to deal with daily stressors in comparison with healthy children<sup>23,24</sup> in addition to the attention and assistance received from achondroplasia supportive organizations.<sup>15,17</sup>

The other questionnaires also revealed impairments in the childhood and adolescent age groups through measurements of functionality (WeeFIM) and pain (APPT). WeeFIM scores were similar across all domains and increased with age, indicating greater independence in older patients. Previous studies evaluating independence in children with achondroplasia suggest that the patients' shortened limbs decrease the functionality of their motor skills and delay their acquisition of developmental milestones, leading to lower scores, especially up to 7 years old, an age range when the children usually start to require less assistance from their parents/caregivers in respect of self-care, such as showering, brushing teeth, and getting dressed.<sup>14,15,22</sup> The reduced motor functionality is also correlated to pain, and, indeed, our results from the APPT questionnaire revealed that more

than 50% of adolescent participants experienced at least 1 pain site, mainly in the knees and shoulders. The LIAISE study reported 3 times more participants with 3 or more pain sites and higher total pain scores.<sup>17</sup>

Pain has also been correlated with impaired physical function in adults.<sup>14</sup> Ten percent of adults included in LISA reported 3 or more pain sites, with the lower spine, shoulder, knees, and thigh being the most cited sites. The majority of the adult population classified the pain as moderate or severe. These findings are consistent with the reports of adult patients experiencing difficulties in standing for long periods, reaching for things, and losing energy in the NHP inventory.<sup>8,9</sup> Other studies correlated increased musculoskeletal pain in late adulthood with the poor QoL reported by older age groups when compared with average-statured individuals and also with children/adolescent/young adults with achondroplasia.<sup>14</sup> In LISA, despite the pain, adults' overall health status was comparable to the reference population, as demonstrated by the comparable EQ-5D-5L index scores. The adult self-rated mean EQ-5D-5L VAS score was lower than the unaffected population, and patients in Brazil reported lower scores than patients from the other LATAM countries participating in the LISA study. This may be related to the anxiety and depression subscale, where higher rates were reported in Brazil. Indeed, patients diagnosed with some psychiatric illness, which represented the majority of a US cohort of adults with achondroplasia, also showed worse physical and mental health status.<sup>25</sup> The NHP reported scores were considered high, indicating poor subjective health status in the adult population, being worse for those who had undergone limb lengthening surgery.

The risk-benefit of performing limb lengthening procedures are controversial among patients with

achondroplasia, caregivers and physicians in terms of height gain and associated risks and complications.<sup>15,26,27</sup> Previous studies that evaluated the effects of lower limb lengthening surgery on physical functioning and QoL assessments in patients with achondroplasia were inconclusive.<sup>14</sup> There were few reports of limb lengthening in the LISA cohort, consistent with other recent reports in the literature for LATAM.<sup>4</sup> The majority of limb lengthened participants were from Colombia, which could be because the Colombian site was coordinated by an orthopedic surgeon. Whereas participants who underwent limb lengthening were more likely to report pain in the knee, lower spine, foot/toes/ankle, and stomach/abdomen, it seems that their functionality and independence tended to improve. However, it is unclear whether this was related to the effects of the limb lengthening surgery itself or the fact that patients undergoing limb lengthening may have had better overall health supervision, leading to better medical care focused on achondroplasia.

Historical medical data from the Argentinean pediatric patients with achondroplasia (PHAS population) were analyzed separately because this was the only site that had access to comprehensive medical records over the reported period. This generated more robust data on medical resource use in the pediatric population. However, the challenges with obtaining medical records for the duration of the retrospective medical history at the other sites means that we cannot make conclusions about the medical burden of achondroplasia in those countries. The main achondroplasia-related medical events reported were in the class of musculoskeletal and connective tissues (78.1% of the events) and ENT disorders (59.4%), knee deformity being the most commonly reported (7.02 event rate per 100 person-years) in the lower age subgroups (<3 and 3-10 years old). These types of event are expected in the achondroplasia population<sup>7,9</sup> and were also observed in the LIAISE study.<sup>17</sup> Both LISA and LIAISE studies found high rates of a broad variety of disease-related complications, particularly at young ages, corroborating with the morbidity rates and prevalence of the multisystemic effects of achondroplasia.<sup>9-11,28</sup> The medical events reported also correlate to the most used medication classes, which were analgesics, anti-inflammatory and antirheumatics.

The high rates of ear disorders in the pediatric population made audiograms the most commonly reported medical examination in <10 years old population. High frequency of HCP visits was found, and several HCP specialties were visited, especially physiotherapists, pediatricians, ENT physicians, and/or surgeons, highlighting the multidisciplinary disease follow-up (also described as the main reason for HCP visits). Hospital visits were generally because of ENT issues, genu varum/valgum, and limb lengthening procedures. With respect to surgeries, 75% of the PHAS population reported at least 1 surgery and the most common types of surgery were adenotonsillectomy, myringotomy, adenoidectomy, and osteotomy, which are consistent with the pathology of achondroplasia and in accordance to the practical guidelines of management of ENT complications requiring surgery.<sup>29,30</sup>

These data suggest the burden of the disease in younger patients intensifies the need for health system use.

Despite the limitations of the LISA study, namely, the differences between the investigator specialties and treatment models of the sites participating in the study, and the diversity of patients enrolled, the results of the assessments undertaken using the HRQoL, WeeFIM, and pain questionnaires were similar across the sites, indicating that patients living with achondroplasia experience a significant burden of illness across multiple domains and a reduced QoL compared with healthy individuals. The LISA data showed that achondroplasia is associated with multisystem complications, pain, and discomfort, which affect QoL, functionality, and the independence of individuals living with the disease.

## Conclusions

The LISA study addressed gaps in the knowledge about the clinical and socioeconomic burden of the illness, HRQoL, the psychosocial impact, and health care resource use, and provided the largest data set to date of individuals with achondroplasia in Latin America. Although this study was not a longitudinal lifetime impact study, the 3-year assessment of retrospective and cross-sectional data and information collected from the patient-reported outcomes in respect of QoL and psychosocial capability demonstrated that patients with achondroplasia experience a significant burden of the disease. These data can help to improve the overall understanding of the impact of achondroplasia on the individuals living with disease, supporting the development of regional strategies to increase access to medical care and adjust management practices as a way to improve patients HRQoL by decreasing the existing burden, especially with increased availability of disease specific treatment options.

## Data Availability

The data sets for the study presented in this publication may be available from the corresponding author upon request.

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## Ethics Statement

The study was conducted in compliance with the Declaration of Helsinki and all current local regulations. The study sites received local independent ethics committee approval. At the Argentinean center the ethics approval was given by Hospital de Pediatría Garrahan Institutional Review Board (IRB; approval number 1140). The Ethics Committee for Analysis of Research Projects of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (CAPPesq; CAAE: 05599519.5.2001.0068) and the Research Ethics Committee from the Fernandes Figueira (CAAE: 05599519.5.1001.5269) approved the research in Brazilian centers. In Colombia, the Clinical Research Ethics Committee of the Institute of Cardiology of the Fundación Cardioinfantil approved the study (Act no. 02-2019). The included patients or, in the case of minors, their parents/

caregivers/legal representatives provided informed written consent.

## Conflict of Interest

Juan Llerena Jr has received consultancy and research grants, speaker fees, and travel support from BioMarin. Pablo Rosselli has received speaker fees and travel support from BioMarin. Amanda Aragão has received travel support from BioMarin. Debora Bertola has participated as a clinical trial investigator. Mariana del Pino has received speaker fees from BioMarin and participated as a clinical trial investigator. Nicolette Calvacanti has received research grants from BioMarin. Jeanne M. Pimenta, Shelda Cohen, Tom Butt, José C. Thomaz Jr, Renée Shediach, Richard Rowell, and Tatiana S.P.C. Magalhães, who are full-time employees of BioMarin, hold stocks in the company. Chong Kim has received travel support from BioMarin. Virginia Fano has received speaker fees from BioMarin and participated as a clinical trial investigator. All other authors declare no conflicts of interest.

## Additional Information

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